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Connecting Autoimmunity and Immunodeficiency Through Mutations of CTLA-4: A Literature Review

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Abstract

Researchers consider autoimmune disorders and immunodeficiencies to be two completely unrelated conditions. However, it has been shown that patients can develop both diseases in spite of opposing etiologies. This has led researchers to examine the commonalities between autoimmunity and immunodeficiency in terms of pathogenesis, clinical manifestations, treatments and, more recently, genetics. Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) is encoded by the CTLA gene and is known for its immunoregulatory role in terminating immune responses. CTLA-4 directly regulates the development of T cells by activating T regulatory cells, but it can also affect the development of B cells in downstream effects. However, it is unclear how CTLA-4 can induce both autoimmunity and immunodeficiency within patients. In this literature review, we show that heterozygous mutations of CTLA-4 can lead to patients developing both autoimmune and immunodeficiency manifestations such as hypogammaglobulinemia, autoimmune cytopenia, lymphoproliferation, and autoimmune enteropathy. Such mutations point toward commonalities in both autoimmunity and immunodeficiency, leading researchers to believe that these two diseases are more alike than different. With this newfound discovery, treatments can be developed to target the CTLA-4 gene in hopes of treating both autoimmunity and immunodeficiency in patients.

Keywords: Autoimmunity, immunodeficiency, CTLA-4, musculoskeletal diseases, genetic diseases.

Introduction

Autoimmune disorders and immunodeficiencies have long been considered mutually exclusive due to their conflicting causes, which has puzzled researchers and greatly affected patients. Autoimmune diseases are caused by damage done to the body by the immune system, while immunodeficiencies are caused by a lack of certain immune cells. Yet recent research and trends have shown that a single patient can develop both diseases simultaneously. Recent studies have shown that 26.2% of patients suffering from primary immunodeficiencies will develop autoimmune and/or autoinflammatory symptoms in their lifetime (Schmidt et al. 2018). In patients, autoimmune cytopenias are the first symptoms indicative of autoimmunity. Autoimmune cytopenias are a condition where the immune system destroys platelets, red blood cells, neutrophils, etc. resulting in blood disorders like anemia. These can later develop into autoimmune enteropathy, arthritis, interstitial lung disease, alopecia, and lesions of the central nervous system (Walter et al. 2019). One study examined the connection between common variable immunodeficiency (CVID) and rheumatoid arthritis (RA). It was determined that in both diseases, there were high levels of $CD21^{-/lo}$ B cells which can contribute to the development of autoreactive B cells resulting in both CVID and RA symptoms (Isnardi et al. 2010).

The concurrence of both disorders likely stems from genetic factors such as heterozygous or homozygous mutations linked to immune dysregulation. These can contribute to defects in immune function relating to T regulatory (T_{reg}) cells, tissue damage leading to excessive antigen load, and defects in thymic selection of T cells during development (Fox 2018;

Schmidt et al. 2018). The connection between autoimmunity and immunodeficiency is further understood through the knowledge of T cells and their pathways in the immune system, especially those involving T-cell signaling and its downstream effects. This leads researchers to believe that the two diseases must share common mechanisms in terms of immune cell activation and/or proliferation, immune system regulation, or complement pathways (Amaya-Uribe et al. 2019).

The control and management of the immune system lies in the human genome. For this reason, genetic mutations have been the focus of many studies trying to determine the causes of both autoimmunity and immunodeficiency. One gene that has taken center stage in the conversation is cytotoxic T-lymphocyte associated protein 4 (CTLA-4), due to its direct control of the T-cell response through T_{reg} cells and other downstream effects (Hosseini et al. 2020). It has been discovered that mutations of CTLA-4 lead to autoimmune symptoms in patients suffering from primary immunodeficiencies such as autoimmune cytopenia, respiratory manifestations, enteropathy, and neurological manifestations among others (Walter et al. 2019). The intention of this review is to implicate mutations of CTLA-4 in the mechanisms of both primary immunodeficiencies and autoimmune disorders and to discuss current and potential treatment options for patients suffering from both diseases.

Description

Immunodeficiency

A patient who has been diagnosed with some form of immunodeficiency shows a sharp decrease in the number of immune cells circulating the body, hence the term immunodeficient. Immunodeficiencies fall under two categories depending on the cause: primary

immunodeficiencies (PIDs) or secondary immunodeficiencies (SIDs). SIDs are more common and therefore better understood than PIDs. SIDs are typically defined as transient or persistent immune cell impairments caused by outside forces unrelated to immune pathways. Some examples include viral or bacterial infection, malnutrition, environmental factors, immunosuppression treatments, stress, etc. Genetics can occasionally cause SIDs, but these are rarer and are still caused by other extrinsic forces (Tuano et al. 2021). For this reason, PIDs are at the center of the autoimmunity and immunodeficiency connection.

PIDs occur when a malfunction of either the adaptive or innate immune systems cause a decrease in certain immune cells, which can lead to immune dysregulation and/or a susceptibility to infection. A few examples of PIDs include common variable immunodeficiency (CVID), chronic granulomatous disease (CGD), and leukocyte adhesion deficiency (LAD) (Devonshire and Makhija 2019). PIDs can also be classified as combined immunodeficiencies (CIDs) because of the many ways the immune system is affected. For example, a patient may develop antibody and immunodeficiency syndromes, such as an inability to produce memory cells, and innate immunity defects, like the development of severe allergies. A patient may also develop severe combined immunodeficiency (SCID) once they begin to develop severe T-cell and B-cell deficiencies in terms of function and absence. A patient diagnosed with SCID can suffer from rash, chronic diarrhea, frequent infections caused by bacteria or viruses, and/or a failure to thrive.

Treatments of both primary and secondary immunodeficiencies focus on supplementing the immune system through immunoglobulin replacement therapies such as intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG) (Tuano et al. 2021). IVIG and

SCIG are given to patients to restore serum levels of immunoglobulin G (IgG), the most common antibody in the body. IVIG is given intravenously at an infusion clinic while SCIG is given subcutaneously either in a clinic or at home. Both treatments are effective at replacing levels of IgG but unfortunately cannot replace any of the other antibodies: IgE, IgM, IgA, and IgD. This is because the other forms of immunoglobulin cannot be as easily extracted from donated blood plasma and do not last as long outside of the body as IgG (Wasserman 2019). These treatments only help the side effects of immunodeficiencies but not their direct causes. Not much is known about the causes of immunodeficiencies, and researchers have only recently begun to understand some of the genetic factors leading to primary immunodeficiencies.

Primary immunodeficiencies can be caused by inborn errors of immunity (IEIs), a list of identified genetic defects associated with disease. In recent years, more than 400 defects have been identified and recognized by the International Union of Immunological Societies (IUIS), which explain the mysterious clinical manifestations of some PIDs such as autoimmunity. With the connection between PIDs and genes, new treatments have been developed or are in development for the targeted treatment of PIDs and the genetic defects that cause them. Bucciol and Meyts (2020) identified a few treatments, such as JAK/STAT[1] pathway inhibitors (Jakinibs), selective inhibitors of PI3Kδ[2], anti-IFN-γ[3] therapy, and, more importantly, CTLA4-IgG[4] fusion protein therapy. Jakinibs target the JAK/STAT pathway that is responsible for the activation of STAT1 and STAT3. It has been shown that gain of function mutations in both STAT1 and STAT3[5] can result in autoimmunity, lymphoproliferative disorder, immune dysregulation, etc. So, by blocking the pathway, the patient's symptoms can be treated effectively. PI3Kδ inhibitors aid in stabilizing a patient's symptoms and overall well-being by reducing IgM,

[1] Janus Kinase (JAK) signal transducer and activator of transcription (STAT), pathway involved in cancer; [2] phosphoinositide-3-kinase delta, receptor used in the JAK/STAT pathway; [3] anti-interferon gamma, signal protein used in the JAK/STAT pathway; [4] cytotoxic T-lymphocyte antigen 4- immunoglobulin G, combination of CTLA-4 and IgG antibody; [5] signal transducer and activator of transcription 1 and 3, parts of the JAK/STAT pathway.

inflammatory cytokines, and senescent T cells. Finally, CTLA4-IgG fusion proteins work to restore the checkpoint balance in CTLA-4 deficient patients who suffer from CTLA-4 haploinsufficiency. Specifically, CTLA4-IgG fusion proteins can restore function to T_{reg} cells and therefore alleviate, or partially alleviate, the symptoms of CTLA-4 haploinsufficiency such as autoimmune, lymphoproliferative, and inflammatory symptoms (Bucciol and Meyts 2020). The targeting of these genes in their respective treatments implicates them as potential suspects for genetic defects in the pathogenesis of PIDs.

Autoimmunity

When discussing autoimmunity in patients, it is important to make distinctions between an autoimmune disorder and autoinflammation. Both disorders share common symptoms, but they can have different causes. Autoimmune disorders are characterized by the immune system's inability to recognize self-antigens and to activate T cells and B cells that attack the body in response, eventually leading to tissue damage. These are known as auto-reactive cells or autoantibodies. Autoinflammatory disorders feature the opposite: autoantibodies are not produced, and the immune system can still function relatively normally, while there is still systemic inflammation present in the body. Autoimmune disorders stem from malfunctions of the body's adaptive immune system, while autoinflammation stems from external environmental forces such as infection, temperature change, and mechanical stress (Szekanecz et al. 2021). This is similar to the difference between PIDs and SIDs.

Both autoimmune and autoinflammatory disorders fall into the category of rheumatic musculoskeletal diseases (RMDs). Naturally, any corresponding disorders fall onto a spectrum of RMDs, with one end representing autoinflammatory disorders called monogenic (single gene) systemic autoinflammatory diseases (SAIDs), and the other end representing autoimmune disorders. Autoimmune disorders are highly diverse yet fall into two categories: systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS). A few examples of autoinflammatory disorders are gout, spondylarthritis (SpA), systemic juvenile idiopathic arthritis (sJIA), and Schnitzler syndrome.

Examples of autoimmune disorders include rheumatoid arthritis (RA), systemic sclerosis (SSc), primary Sjögren syndrome (pSS), and idiopathic inflammatory myopathies (IIMs) (Szekanecz et al. 2021). These diseases, and others, can be categorized as either autoimmune, autoinflammatory, or mixed pattern (Fig. 1).

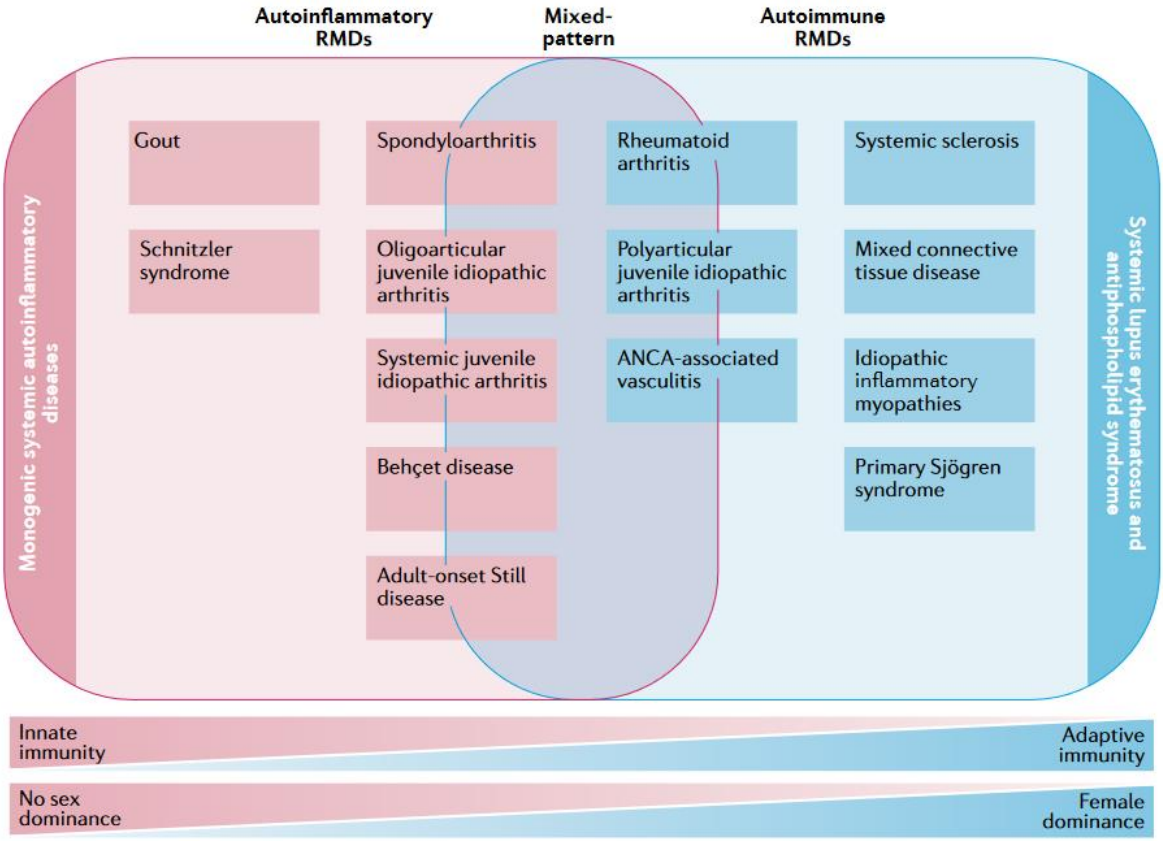

Fig. 1 | Spectrum of autoinflammatory, mixed-pattern and autoimmune diseases. Prototypes of a classical autoinflammatory disease are the group of monogenic systemic autoinflammatory diseases known as periodic fever syndromes (pink). Prototypes of classical autoimmune disease are systemic lupus erythematosus and antiphospholipid syndrome (blue). Diseases in the middle of the spectrum might be considered mixed-pattern rheumatic and musculoskeletal diseases (RMDs; mixed color). Indicated by the spectra at the bottom of the figure, classical autoinflammatory conditions are characterized by a predominance of innate immunity and have no sex dominance. By contrast, classical autoimmune conditions are associated with more prominent adaptive immune responses and female dominance. ANCA, antineutrophil cytoplasmic antibody (Szekanecz et al. 2021, Fig. 1).

By following SLE and SAID as models for autoimmunity and autoinflammation, respectively, a definition for both diseases can be based on their cellular processes. In SLE, over 100 autoantibodies can be produced in various organs while lots of T- and B-cell activation occurs. In contrast, monogenic SAIDs are predominantly caused by an overactive innate immune

system which can cause fevers in patients who are not diagnosed with an infection (Szekanecz et al. 2021). Overall, though there are some clear distinctions between autoimmunity and autoinflammation, they are not mutually exclusive, as some common autoimmune disorders like RA follow a mixed-pattern list of symptoms. This relationship is similar to that of autoimmunity and immunodeficiency and therefore has some potential basis in genetics.

The treatments for both autoinflammatory and autoimmune diseases vary because they are designed to treat different immune system pathways. Autoinflammatory disorder treatments are designed to block the cytokine cascade that causes the inflammation in these disorders. Such treatments include recombinant IL-1RA[6] (anakinra), anti-IL-1β[7] antibody (canakinumab), and recombinant IL-1R[8] fusion proteins (rilonacept). In general, IL-1 inhibitors

[6] interleukin 1 receptor antagonist, inhibits IL-1 receptor; [7] anti-interleukin 1 beta, antibody that attacks IL-1; [8] interleukin 1 receptor, receptor that binds IL-1.

are used for a variety of autoinflammation disorders and have shown great efficacy in patients. The primary targets for treatment of autoimmune diseases include T cells, B cells, and cytokines due to their contribution to disease. One treatment (rituximab) is a B-cell inhibitor that has been used to treat a broad spectrum of autoimmune diseases such as SLE and SSc. Another treatment that has been approved to treat specific forms of autoimmune disease is abatacept, or CTLA4-IgG fusion protein, which has shown efficacy in inhibiting T cells. Lastly, in mixed-pattern RMDs, jakinibs (JAK/STAT pathway inhibitors) have been used to treat RA and SpA. There is evidence to suggest that jakinibs could also treat SLE and monogenic SAIDs (Szekanecz et al. 2021). The one treatment that stands out is abatacept, which is also used to

treat patients with immunodeficiency. This suggests that a single treatment (medication or intravenous infusion) could treat not only immunodeficiency but also autoimmunity.

Synthesis

CTLA-4

Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) is an immunoregulator that is responsible for terminating the immune response and the activation of T regulatory (T_{reg}) cells. Although the mechanism is not fully understood, it is known that CTLA-4 negatively regulates T-cell activation by competitively binding to B7.1 and B7.2 with CD28 which share the same ligands. CD28 and CTLA-4 are similar in structure but work in opposite ways. CD28 triggers an immune response through T-cell stimulation and proliferation. CTLA-4 terminates an immune response by stopping T-cell expansion, which therefore halts T-cell response and replication. There are many other mechanisms that CTLA-4 uses to impact the immune response, such as the inhibition of T-cell proliferation and T-cell differentiation. Even though CTLA-4 directly affects T-cell activation, it can also modulate B-cell and antibody production. CTLA-4 does so by inhibiting T follicular (T_f) and T follicular regulatory (T_{fr}) cell differentiation and expansion. If both T_f and T_{fr} cells are inhibited, then B-cell expression of CD80 and CD86 (surface proteins) is also inhibited (Hosseini et al. 2020). It is clear that CTLA-4 plays a major role as an immunoregulator. Therefore, it is more than reasonable to implicate CTLA-4 as a culprit in explaining why a patient can develop both autoimmunity and immunodeficiency.

To further understand CTLA-4 as an immunoregulator responsible for terminating the response, mice lacking CTLA-4 (-/-) were studied. In this study, it was first discovered that mice

deficient in CTLA-4 died prematurely around 3-4 weeks of age, leading researchers to believe that the CLTA-4 (-/-) phenotype is deadly. Through histologic and immunohistologic analysis, it was revealed that CLTA-4 (-/-) mice showed a massive proliferation and infiltration of lymphocytes, neutrophils, and macrophages, resulting in myocarditis and pancreatitis. Some mice were even observed to have developed vasculitis and synovitis. The proliferation of immune cells into the body is what causes them to infiltrate organs such as the heart and pancreas. The researchers suggest that this is because of CTLA-4's role as a negative immunoregulator. CTLA-4 can halt the immune response by deactivating T cells through apoptosis (cell death) and even deleting autoreactive cells in the thymus (Tivol et al. 1995). CTLA-4 is crucial in maintaining immune cell homeostasis to ensure that T cells do not run rampant through the body resulting in massive amounts of lymphoproliferation and eventual organ infiltration, as described in this study.

Additionally, several cohort studies have been done on extended families with known immunodeficiencies in their family history to associate mutations in CTLA-4 to their diagnoses. One such study involved a cohort of 23 people from four different families, each with a suspected CTLA-4 mutation. The researchers first performed exome and Sanger sequencing on the participants and discovered heterozygous mutations (+/-) of CTLA-4 in these participants. Each of the four families had their own unique CTLA-4 mutation at different positions on the gene (Kuehn et al. 2014) (Fig 2).

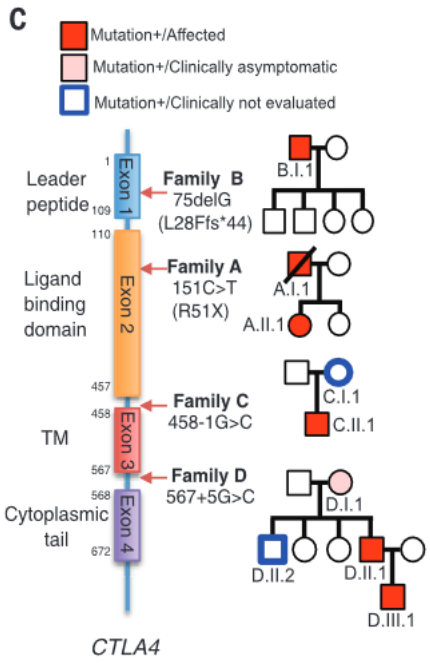

Fig. 2 | Clinical phenotype and pedigree of the patients. **(C)** Mutations in patient alleles displayed on a schematic of the four exons of CTLA-4, pedigrees, and phenotype summary highlighting organs (gray) with inflammatory infiltrates and autoimmune cytopenias for affected family members. TM, transmembrane domain (Kuehn et al. 2014, Fig. 2).

Patients affected by a mutation of CTLA-4 had reduced CTLA-4 mRNA and protein expression on T_{reg} cells which persisted even after T_{reg} activation, indicating that T_{reg} dysfunction was a commonality among all patients with a heterozygous CTLA-4 mutation. This study was also able to corroborate conclusions given by Tivol et al. (1995), that mutations of CTLA-4 can lead to massive lymphoproliferation (hyperproliferation, as Kuehn et al. [2014] described it) compared to healthy donors. It was also discovered that heterozygous mutations of CTLA-4 can lead to reduced frequencies of B cells. Patients with a heterozygous mutation of CTLA-4 showed increased blood levels of $CD21^{lo}$ cells, indicating an exhausted state. Because of $CD21^{lo}$ exhaustion, there was heightened B-cell apoptosis and reduced B-cell receptor-induced proliferation (Kuehn et al. 2014). $CD21^{lo}$ B cells play an important role in the pathogenesis of common variable immunodeficiency (CVID). CVID $CD21^{lo}$ cells have been shown to be

polyclonal, partially autoreactive, etc., making them distinct from other B cells (Rakhmanov et al. 2009).

A potential reason why CTLA-4 deficient patients develop hypogammaglobulinemia (low numbers of antibodies) and B-cell lymphopenia (lack of B cells) are because of B-cell abnormalities (Kuehn et al. 2014). Another cohort study of five families corroborates the findings that heterozygous mutations of CTLA-4 are responsible for T_{reg} cell suppression, lymphocytic organ infiltration and hyperproliferation, and reduced B cells in blood (Schubert et al. 2014). Heterozygous mutations of CTLA-4 can lead to a variety of symptoms in patients that appear to stem from either hyperproliferation of lymphocytes or reduced levels of specific immune cells such as T_{reg} or B cells. With this information, a connection between autoimmunity and immunodeficiency can form based on mutations of CTLA-4.

To begin connecting autoimmunity and immunodeficiency, 133 patients with known CTLA-4 insufficiencies were studied to determine their clinical phenotypes, or what medical complications each patient had. An overall clinical phenotype for the participants were infections, autoimmunity, and lymphoproliferation, all three affecting various organ systems (Schwab et al. 2018). Several other symptoms were reported by patients suffering from CTLA-4 insufficiency that affect different body systems in a variety of different ways (Fig 3).

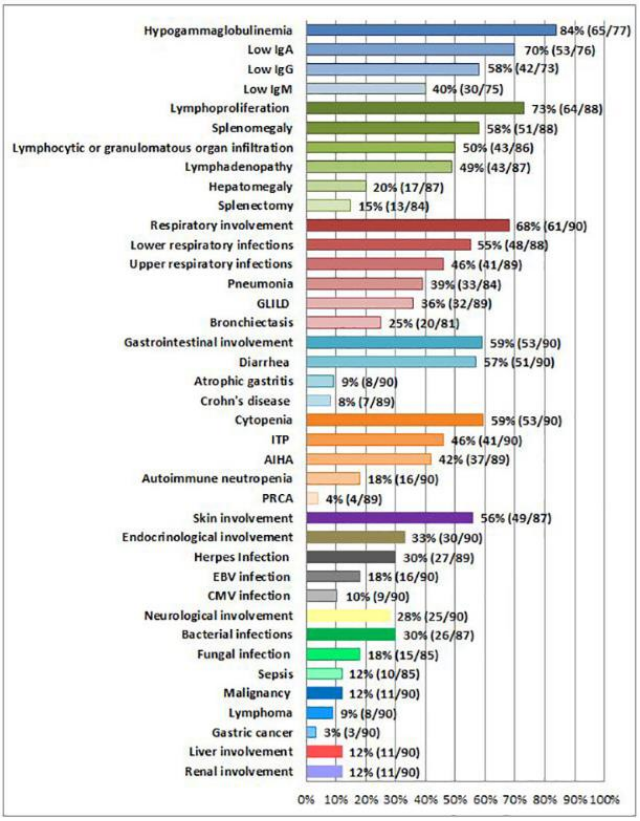

Fig. 3 | Main clinical findings in CTLA-4 insufficiency percentage distribution of clinical manifestations within affected mutation carriers. Clinical data was available for 71 to 90 affected mutation carriers (Schwab et al. 2018, Fig. 3).

This study was also able to identify 45 unique, heterozygous, germline mutations of CTLA-4

among the participants (Fig 4).

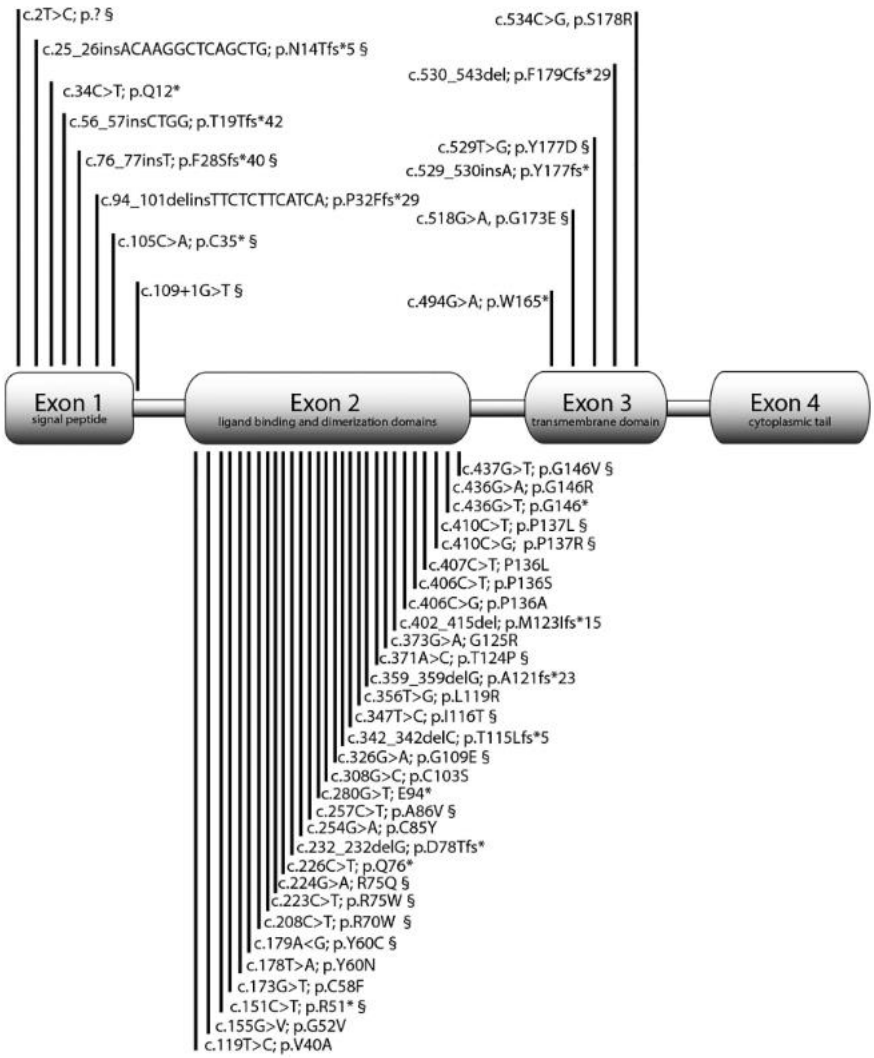

Fig. 4 | Heterozygous germline mutations within the CTLA-4 gene are distributed throughout exon 1–3. The distribution of the heterozygous germline mutations throughout the CTLA-4 gene. Eight mutations are located in exon 1, 31 are located in exon 2, and six are located in exon 3. Mutation was functionally tested by transendocytosis assay (Schwab et al. 2018, Fig. 4).

A few studies have implicated heterozygous mutations of CTLA-4 in autoimmunity, specifically Crohn's disease (CD) and rheumatoid arthritis (RA). Zeissig et al. (2015) conducted a study on patients presenting with Crohn's disease, as well as suspected mutations of CTLA-4. The researchers were able to identify a specific mutation, *CTLA-4 Y60C*, in these patients who were also diagnosed with some forms of autoimmunity, such as autoimmune cytopenias, type-I

diabetes mellitus, or chronic sinusitis. By examining the immunological phenotype of each patient, researchers concluded that there is a possible causal relationship between CTLA-4 mutations and autoimmunity, although the specific pathways remain unclear (Zeissig et al. 2015).

Two studies have examined the correlation between CTLA-4 and rheumatoid arthritis, one representing a population in the United Kingdom and the other a Chinese Han population. In the former, five single nucleotide polymorphisms (SNPs) of CTLA-4 and two SNPs related to autoimmunity were examined in 122 patients. It was determined that there was no connection between RA and CTLA-4 SNPs despite thorough genotyping (Barton et al. 2004). The latter study, done on Chinese Han patients, used similar methods to the Barton et al. study but examined different SNPs. This study determined that there was a correlation between CTLA-4 SNPs and RA even in a meta-analysis comparing their results to other populations around the world, corroborating this finding (Lei et al. 2005, Table 1).

	Distribution of CTLA-4 +49 genotype						*Frequency of CTLA-4 allele*				
	GG		*GA*		*AA*		*G*		*A*		
Study	*Case*	*Con*	*Case*	*Con*	*Case*	*Con*	*Case*	*Con*	*Case*	*Con*	*OR (95%)*
European											
Seidl C *et al* (1998)	37	68	138	210	83	178	212	346	304	566	1.14 (0.91–1.43)
Gonzalez-E MF *et al* (1999)	10	30	63	103	65	172	83	163	193	447	1.18 (0.85–1.63)
Barton A *et al* (2000)-UK	38	19	86	51	68	26	162	89	222	103	0.85 (0.59–1.22)
Barton A *et al* (2000)-SP	14	12	57	70	65	62	85	94	187	194	0.94 (0.65–1.36)
Milicic A *et al* (2001)	63	73	223	213	135	166	349	359	493	545	1.07 (0.88–1.31)
Vaidya B *et al* (2002)	20	45	65	158	38	146	105	248	141	450	1.35 (1.00–1.84)
Barton A *et al* (2004)	34	29	55	68	43	59	123	126	141	186	1.29 (0.91–1.82)
Asian											
Matsushita M *et al* (1999)	200	56	199	72	62	22	599	184	323	116	1.17 (0.88–1.54)
Yanagawa T *et al* (2000)	29	78	50	88	6	34	108	244	62	156	1.21 (0.82–1.80)
Lee YH *et al* (2002)	41	49	35	29	10	8	117	127	55	45	0.75 (0.46–1.23)
Lee CS *et al* (2003)	103	85	67	100	16	18	273	270	99	136	1.39 (1.01–1.92)
Liu MF *et al* (2004)	14	21	42	50	9	10	70	92	60	70	0.89 (0.54–1.45)
Present study	148	86	138	125	40	39	434	297	218	203	1.36 (1.06–1.74)
African											
Hadj KH *et al* (2001)	23	68	27	62	10	20	73	198	47	102	0.80 (0.51–1.27)

OR (95% CI): odds ratio (allele G *versus* allele A) and 95% confidence interval; Con: control.

Table 1 (Table 5 from Lei et al. 2005) | Distribution of CTLA-4 +49 genotypes and frequency of alleles for RA patients and controls (Lei et al. 2005).

These studies present opposing conclusions to the correlation of RA and CTLA-4. They are also somewhat outdated and subject to new information found in the last ten years. Their results cannot be completely ruled out, however, because both studies examined different SNPs. There is a case, however, for CTLA-4 to be implicated in the pathogenesis of RA since there is a clear connection between it and other autoimmune symptoms, but more research needs to be done to come to a clear conclusion.

Conclusions and Future Directions

There has long been an understanding that patients can develop immunodeficiency and autoimmune disorders at the same time, despite their seemingly opposing etiologies. Evidence suggests that instead of being opposites, they are in fact two sides of the same coin (Schmidt et al. 2018). Several factors connect the two diseases, but at the center of them all is genetics. There have been several genetic mutations associated with both immunodeficiency and autoimmunity, but CTLA-4 is a gene that specifically interests researchers (Walter et al. 2019). CTLA-4 regulates the immune response by activating T regulatory cells. T_{reg} cells work to maintain immune homeostasis by keeping the levels of T and B cells in balance as well as keeping levels of autoreactive B cells in check (Hosseini et al. 2020).

If CTLA-4 is mutated, there are significant consequences downstream in the immune response. Such mutations can result in CTLA-4 haploinsufficiency where patients can develop T-cell deficiency, hypogammaglobulinemia, and autoimmune cytopenia, as well as features that affect the respiratory, gastrointestinal, and neurological systems (Schwab et al. 2018). CTLA-4

haploinsufficiency stems from CTLA-4 not binding to its ligand, which causes T_{reg} cells to malfunction and throws the immune system out of homeostasis. This one connection has serious implications in terms of downstream effects, even resulting in B-cell deficiency (Kuehn et al. 2015; Schubert et al. 2015; Schwab et al. 2018). It can be assumed that CTLA-4 plays a role in the development of both autoimmunity and immunodeficiency, which could explain why patients can present with both. Either a heterozygous or homozygous mutation of the CTLA-4 gene raises the chances of a patient developing both diseases, which can ultimately result in lower life expectancy and lower quality of life.

Currently there is no well-known treatment that can treat both an autoimmune disorder and immunodeficiency; there are only treatments for each individual disease. There are some current treatments that can help with CTLA-4 haploinsufficiency, such as hematopoietic stem cell transplant or immunoglobulin replacement therapy (Slatter et al. 2016; Egg et al. 2022). But the former comes with great risks while the latter addresses only one of the many clinical manifestations of CTLA-4 haploinsufficiency. Future research should focus on developing a treatment that can help undo the effects of a CTLA-4 mutation by aiding the immune system. Immunotherapies have been developed as cancer treatments by blocking certain immune pathways such as the CTLA-4 mechanism, for example Ipilimumab, which block CTLA-4 from binding to B7.1 and B7.2, thereby blocking the negative regulation of an immune response. This treatment has been shown to affect multiple pathways of the immune system, leading to remission in cancer patients (Zhang et al. 2021). At the same time, while this immunotherapy blocks the CTLA-4 pathway, there is potential for it to stimulate the CTLA-4 pathway in CTLA-4

deficient patients. This sort of treatment could help treat both the autoimmune and immunodeficient aspects of CTLA-4 haploinsufficiency.

Lastly, further research needs to be done on understanding if there are more genetic mutations that could be potential culprits for the development of both immunodeficiencies and autoimmune disorders. Such genes code for important immune system proteins including NFkB, the Jak-STAT pathway, and IL2/IL21. Expanding our knowledge of how genetic mutations affect the immune system will give researchers a better understanding of how the immune system works to ultimately unlock the human immunome. It is also crucial to continue to investigate CTLA-4 so that researchers can answer some of the questions about how CTLA-4 mutations cause both autoimmunity and immunodeficiency.

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