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Review

Cytotoxic T-lymphocyte Associated Antigen-4 (CTLA-4) Polymorphism, Cancer, and Autoimmune Diseases

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Abstract: Immune system dysfunction is one of the key features in onset and development of cancer and autoimmunity. Cytotoxic T-lymphocyte-antigen-4 (CTLA-4), as a leader immune checkpoint plays a crucial effects in the regulation of immune suppression and tolerance. In this review, role of CTLA-4 and its three important polymorphisms (SNP), CTLA-4 +49A/G, CTLA-4 CT60 A/G and CTLA-4 −318C/T in development of cancer and autoimmune diseases have been discussed. The evidences revealed that CTLA-4 +49A/G, A allele increases the risk of cervical cancer and CTLA-4 +49A/G G allele decreases the risk of breast cancer in Asian population. The presence of G allele of CTLA-4 +49A/G SNP is strongly correlates with increased risk of Graves and systemic lupus erythematous (SLE), in Asian and European population. G allele of CTLA-4 +49A/G SNP may be a risk factor for rheumatoid arthritis susceptibility (RA). Evidence suggests that the presence of CTLA-4 +49 G allele reduces the inhibitory function of CTLA-4 on T cells. Therefore, it is logical to propose that G allele of CTLA-4 +49 A/G increases the immune system activity and decreases the risk of cancer. The evidence on the effect of CTLA-4 CT60 A/G SNP on the risk of cancer development and autoimmune disorders is inconclusive. No association was found between the CTLA-4 −318C/T polymorphism with autoimmune diseases.

Keywords: CTLA-4; cancer; autoimmunity; polymorphism; Graves

1. Introduction

Immune system dysfunction is one of the key features in onset and development of cancer and autoimmunity [1]. One reason for the development of malignancies is failure of T lymphocytes to recognize tumor-specific antigens. Presentation of antigen to T cell receptor (TCR) by major histocompatibility complex (MHC) proteins is a part of T cells mechanism to eliminate foreign antigen [2–4]. Antigen presentation to T cells alone however, is not enough to achieve effective immunogenic cell death in emerging or progressing malignancies [2]. Complex protein-protein interactions contribute to T cell activation and lead to stimulatory and/or inhibitory signals production, necessary for normal function of the immune system [5].

Interaction of CD28 (Cluster of Differentiation 28) or inducible costimulator (ICOS) [6] receptors from T cell with CD 80 (B7-1) or CD86 (B7-2) ligands from antigen presenting cell (APC) activates T cell, leading to secretion of cytokines [7,8]. T cell activation and excessive expansion of activated T cells is inhibited by negative signals provided by immune checkpoints, cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death 1 (PD-1) [9]. Both CD28 and CTLA-4 receptors bind to CD80 and CD86 with different affinity. CD28 is a highly expressed receptor but has low-affinity for CD80 and CD86 ligands, whereas CTLA-4 is a low abundance receptor with higher-affinity for the ligands [10,11]. CTLA-4 serves as a negative regulator when it is associated with Treg cells and present antigen to T cells when they are expressed by antigen presenting cells [12]. CD28, on the other hand, is constitutively expressed on both resting and activated conventional T cells [13]. The lack of balance between these two receptors leads to malignancy and loss of immune tolerance [14]. It has been shown that inhibition of CTLA-4 results in increased activation of the immune system. This finding has led to new immunotherapies for melanoma [15,16], non–small cell lung cancer, and other cancers [17–21]. Activation of immune system by anti–CTLA-4 monoclonal antibody therapy apparently has improved the melanoma outcomes for cancer patients [22]. Despite many findings (information) regarding mechanisms by which *CTLA-4* regulates T cell response, several studies suggest that genetic factors are involved in susceptibility to autoimmune diseases and malignancy [23–26].

In this mini-review, the mechanism by which *CTLA-4* regulates T cell response and the effect of its gene mutations as associated with autoimmune and cancer susceptibility will be discussed.

2. *CTLA-4* Structure and Function

CTLA-4 (Gene ID:1493, MIM number:123890) is a new member of the immunoglobulin superfamily known as insulin-dependent diabetes mellitus 12 (IDDM 12) [27] and cluster of

differentiation 152 (CD152) [28]. It is mapped to chromosome 2q33 with a nucleotide size of about 6.2 kb and consists of four exons and 3 introns [29]. The CTLA-4 protein consists of a 37 amino acid leader peptide, an extracellular immunoglobulin (Ig) V like domain or the ligand-binding domain (116 amino acid), a hydrophobic transmembrane region (37 amino acid), and a cytoplasmic domain [30–32]. Chistiakov et al. reported that the 5' region of the gene contains a Kozak consensus sequence with the ATG initiation codon, an in-frame stop codon 26 bp upstream of this ATG and a TATA box 75 bp upstream of the stop codon. The 3' untranslated region (UTR) comprises a stretch of almost 30 AT repeats [33].

Three different isoforms of this protein have been identified (1) the surface full-length CTLA-4 (flCTLA-4) protein consisting of 149 amino acids where all four exons have expressed, (2) soluble transmembrane deleted CTLA-4 mutant protein (sCTLA-4), and (3) CTLA-4 mutant protein lacking both extracellular and transmembrane domains [34–36].

CTLA-4 is an intracellular protein that translocates to cell surface through recruitment of enzymes such as GTPase ADP ribosylation factor-1 and phospholipase D [6,17,37]. An association between low expression of the sCTLA-4 and susceptibility to autoimmune diseases, such as Type 1 diabetes has been reported [31,32,38]. Although the importance of CTLA-4 in maintaining immune homeostasis is unquestionable, the mechanism of CTLA-4 function is still unclear. We have summarized several different pathways which have been suggested previously [39].

Both T cell-intrinsic and T-cell extrinsic mechanism have been proposed for CTLA-4 as summarized in Figures 1 and 2 [40]. Carreno and coworkers have predicted that in early stages of immune response which CD80 is expressed at low levels, negative signal generated via CTLA-4 is a primary mechanism for inhibition of T lymphocyte activation. Whereas both CTLA-4 negative signaling through CTLA-4 and CD80 sequestration would be effective during later stages of immune response when CD80 expression is increased by IFN-gamma stimulation [52,53].

$CD4^{+}CD25^{+}FoxP^{3+}$ regulatory T cells are pro-inflammatory effector and anti-inflammatory suppressor cells which have an important role in maintenance of tolerance to self in models of transplantation. Krummey et al. have reported that CTLA-4 negative signals after transplantation were required for $FoxP^{3+}$ Treg suppression and long term graft survival. Moreover, CD28 blocking by reagent causes long-term survival of skin and cardiac allografts and the effect of CD28 blocking depends on signals generated by CTLA-4 [54]. The importance of anti-CTLA-4 therapy, vaccine, chemotherapy and radiation together in various malignancy treatment especially advanced melanoma have been suggested [55,56].

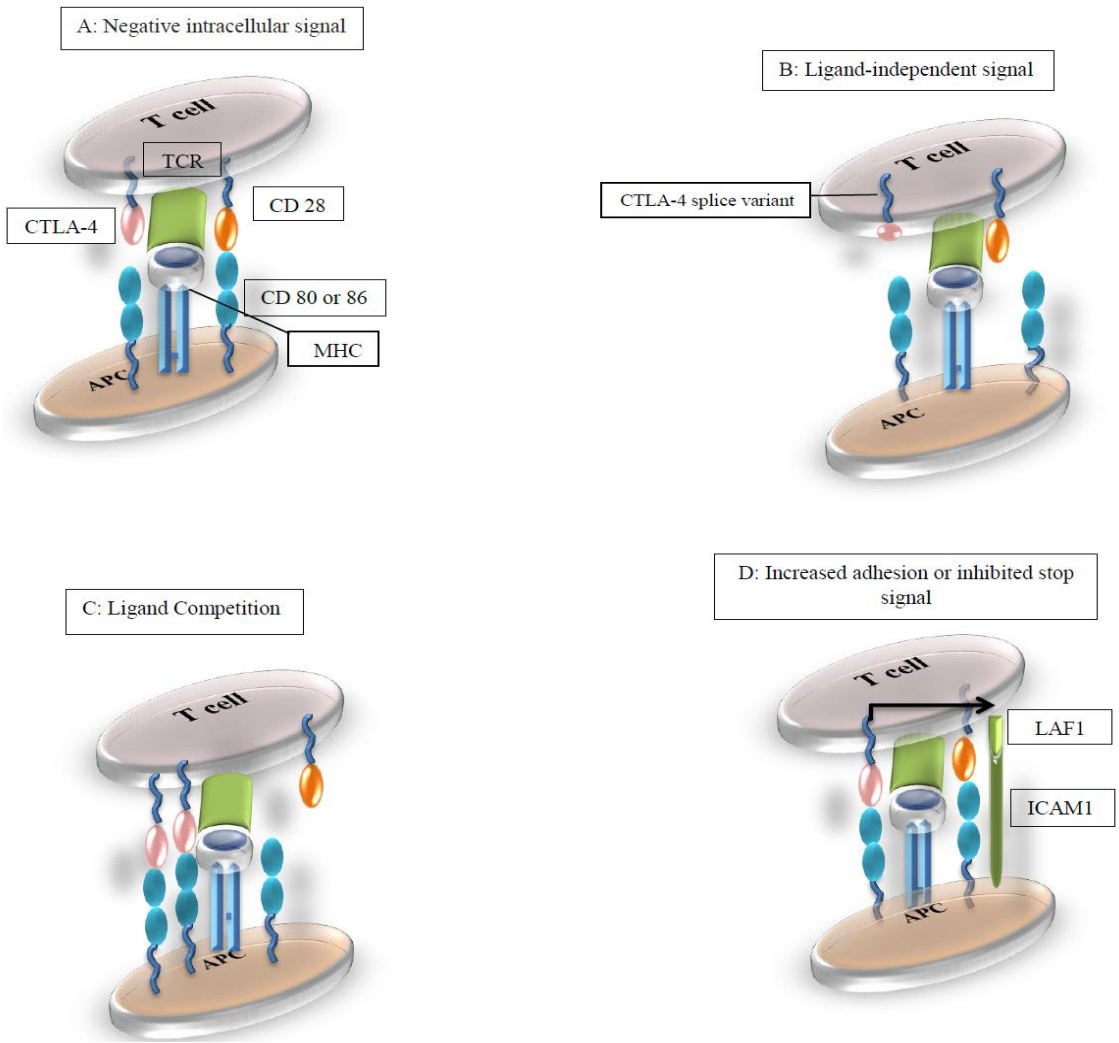

Figure 1. T-cell intrinsic function. (a). CTLA-4 via recruitment of phosphatases such as protein phosphatase 2A (PP2A) decreases the phosphorylation of essential mediators for TCR signaling cascade, including CD3ζ, a transmembrane adaptor signaling protein. Therefore CTLA-4 delivers inhibitory signals which may interfere with stimuli signals generated by T-cell surface receptors such as CD28 [41]. This interferes with stimulatory signals generated by T-cell surface receptors such as CD28. The inhibitory effect of CTLA-4 through alterations in lipid raft location has also been proposed (Figure 1a) [42]. (b). soluble CTLA-4 due to lack of extracellular domain cannot bind ligands, therefore any negative signal is ligand independent [43]. (c) CTAL-4 prevents stimulus signal produced by CD28 through high affinity competition for CD80 and CD86 ligands [44]. (d). CTLA-4 ligation either increases adhesion via lymphocyte function-associated antigen 1 (LFA1) from T cell with intercellular adhesion molecule 1 (ICAM1) from APC or decreases residence time on the APC. So the TCR-mediated 'stop' signal, which is essential for lymphocyte activation is suppressed [45]. APC: antigen presenting cell, TCR: T cell receptor, MHC: major histocompatibility complex, LFA 1: lymphocyte function-associated antigen 1, ICAM 1: intercellular adhesion molecule 1.

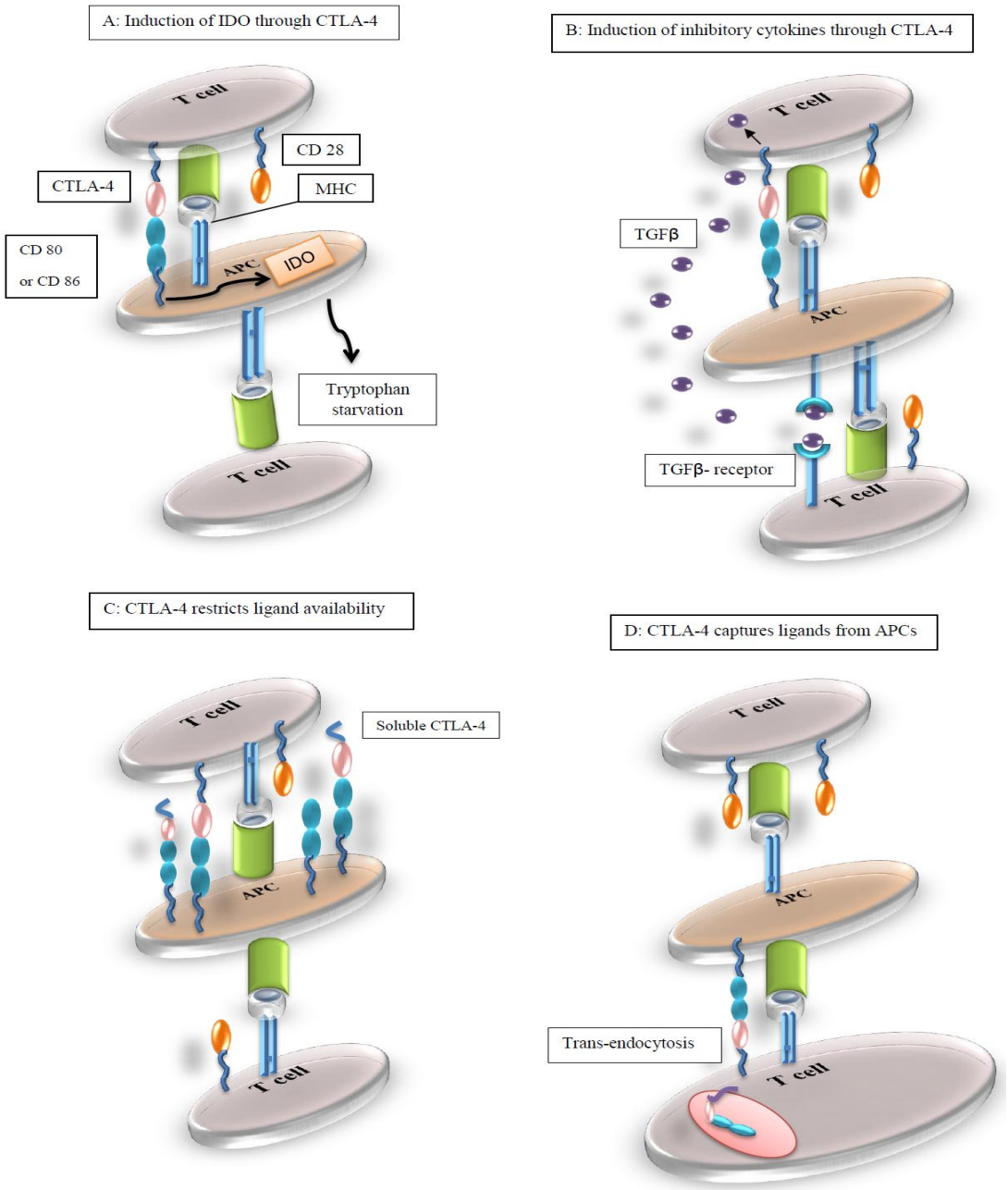

Figure 2. T cell-extrinsic CTLA-4 function. (a). CTLA-4 suppresses T cell proliferation through induction of indoleamine 2,3-dioxygenase (IDO) activity in APCs. It has been shown that IDO suppresses antigen-specific T cell proliferation and permits tumor cells to escape from immune rejection through tryptophan depletion [46–48]. (b). CTLA-4 signals stimulate the production of negative regulators of immune homeostasis such as transforming growth factor β (TGFβ) and interleukin-10 (IL-10) [49] at sites of cell–cell interaction [50]. (c). Soluble CTLA-4 splice variant can be secreted by T cells and its ligation with CD80 and CD86 ligands leads to reach out for CD28 ligation and prevents other T cells from receiving stimulatory signals. (d). Stimulatory capacity of APCs can be blocked by CTLA-4 expression on the surface of T cells. CTLA-4 expression can induce trans-endocytosis of CD80 and CD86 from the opposite cell and consequently it lowers the level of ligands on the surface of APCs [51]. TGFβ: Transforming growth factor-β.

3. CTLA-4 Polymorphism

Seventeen single nucleotide polymorphism (SNP) at positions −1765, −1722, −1661, −1577, −658, −319, 49, 6230, 6249, 7092, 7482, 7982, 8173, 10242, 10717, 12131 and 12310 of CTLA-4 gene has been identified [57,58]. However, the functional role of only a few of the SNPs and their association with susceptibility to diseases are well documented. CTLA-4 +49 A/G SNP in exon 1 leads to alanine to threonine substitution in leader sequence and affects the protein processing in the endoplasmic reticulum (ER), leading to lower effective glycosylation which plays an important role in protein membrane expression [36,59]. Two of the most important CTLA-4 gene variations are G/A nucleotide transition at position -1661 and T/C change at −1722 within the promoter region [60]. T/C change at position −1722 affects binding sites of transcription factors, whereas G/A transition at position −1661 may alter the potential response element for myocyte enhancer factor 2 (MEF2) [61,62]. GG genotype compared with AA at +6230 (CT60) position leads to less expression of sCTLA-4 versus full-length isoform by 50%.

Individuals with AA genotype and high levels of sCTLA-4 were protected against risk of some autoimmune diseases. Moreover +6230 (CT60) AA Vs GG genotype was associated with increased T_{reg} cells levels in peripheral blood. Also the higher promoter activity and the higher expression of membrane CTLA-4 were associated with allelic variant at −318 C/T position in promoter region [36].

In this mini review, the role of CTLA-4 +49 A/G, CT60 A/G, and −318 C/T SNPs in malignancies (Table 1) and autoimmune diseases susceptibility (Table 2) will be discussed.

Table 1. Odds ratio and distribution of cytotoxic T lymphocyte CTLA-4 +49A/G, CT60 A/G and −318 C/T genotypes and alleles in different cancer patients and control subjects.

Reference	Population	Disease	SNP	Patient	control	P	OR
			+49A/G				
Dai/2017	Asia	Breast	G allele	4544	4515	<0.001	0.8
Han/2016		Bone tumors	A vs. G	1003	1162	<0.001	1.36
Jaiswal/2014	India	Bladder	genotypes	200	200		3.74
Gao/2014	Asia	Cancer*	GG vs. AA	16358	19737		0.75
Liu/2014		Cervical	A allele	2835	2560	<0.05	1.16
Minhas/2014	India	Breast	G allele	250	250	0.7	0.9
Qiu/2013		Cervical	GG+AG vs AA			NS	0.94
Khaghanzade /2010	Iran	Lung	Genotype	127	124	NS	NS
Hu/2010	China	Cervical	AA vs GG	719	719		1.66
Hu/2010	China	HCC	AA vs GG	864	864		1.43

Saenz Lopez /2009	Spain	Renal	AA	127	176		
Su/2007	Taiwan	Cervical	Genotype	144	378	NS	NS
Cheng/2006		gastric MALT lymphoma	GG	62	250	0.04	4.1
CT60A/G							
Jaiswal/2014	India	Bladder	Genotype	200	200		1.36
Qiu/2013	Asia	Cervical	GG+AG vs. AA				0.75
Bharti/2012	India	Oral	AA	130	180		3.0
Erfani/2012	Iran	Head & neck	AA	80	85	0.004	0.34
Khaghanzadeh/ 2010	Iran	Lung	Genotype	127	124	NS	NS
Saenz Lopez /2009		Renal	AA	127	176	<0.05	
Perez/2009	Spain	AML relapse	AA	143		0.004	2.64
Su/2007	Taiwan	Cervical	genotypes	144	378	NS	NS
Cheng/2006	Taiwan	gastric MALT lymphoma	genotypes	62	250	NS	NS
−318C/T							
Lu/2016	Asian	malignant tumor	TT+TC vs.CC	3539	4690	<0.05	1.28
Han/2016	China	bone tumors	C vs. T	1003	1162	NS	NS
Jaiswal/2014	India	Bladder	Genotype	200	200	NS	NS
Liu/2014		Cervical	C allele	2835	2560	<0.05	0.79
Qiu/2013	Asia	Cervical	TC vs. CC				2.02
Rahimifar/2010	Iran	Cervical	CC	55	110	0.021	
Khaghanzadeh/ 2010	Iran	Lung	genotypes	127	124	NS	NS
Su/2007	Taiwan	Cervical	Genotype	144	378	0.03	1.99
Cheng/2006	Taiwan	gastric MALT lymphoma	Genotypes	62	250	0.02	0.3

AML: acute myeloid leukemia, NS: no significant, gastric MALT lymphoma: gastric mucosa-associated lymphoid tissue (MALT) lymphoma, HCC: hepatocellular carcinoma, Cancer: cervical cancer, breast cancer, lung cancer, HCC.

Table 2. Odds ratio and distribution of cytotoxic T lymphocyte CTLA-4 +49A/G, CT60 A/G and −318 C/T genotypes and alleles in different autoimmune patients and control subjects.

Reference	Population	Disease	SNP	Patient	control	P	OR
			+49A/G				
Narooie/2017	Iran	Hashimoto's thyroiditis	Genotypes	82	104	NS	NS
Ting/2016	China	Graves'	G allele	289	158	0.001	1.5
Sameem/2015	Pakistani	RA	GG	100	100		3.018
Li/2014*	Asia, Caucasian &Africa	RA	GG vs. AA	9805	10691	<0.05	1.13
Du/2014*	Europe	Graves'	G allele			0.001	1.14
Devaraju/2014	India	SLE	AG & GG	300	460	0.0001	2.29
Liu/2014*	Americas, Europe & Asia	MS		12916	15455	NS	NS
Liu J/2013*	Asia & Europe	SLE	Genotypes	1753	2279	NS	NS
Du L/2013*	China	Graves'	GG+GA				2.57
Zhai/2013*	Asia	SLE	GG+GA			0.04	0.85
Li/2012*	Asia & Europe	RA	GG+AG vs. AA				1.18
Si X/2012*	Asia	Graves'	Genotypes	8288	9372	<0.001	1.6
Farra/2012	Lebanon	thyroid	Genotypes	128	186	NS	NS
Chang/2012*	Asia	SLE	GG vs AA	1806	2490		1.53
Paula/2011	Spain	Graves'	G allele	100	50	0.01	1.9
Kimkong/2011	Thailand	Graves' & SLE	G allele	283	153	NS	NS
Chua/2010	Malaysia	SLE	Genotypes	130	130	NS	NS
Bicek/2009		AITD	GG			0.04	
Khalilzadeh/2009	Iran	Graves'	GG	105	103	0.005	6.000
Chong/2008	China	Graves'	GG	177	151	0.005	
Balbi/2007	Italy	SSc	G allele	43	93	0.07	
Greve/2007	Germany, Hungary & Poland	MS	Genotypes			NS	NS
Han/2006*	China	Graves'	Genotypes			NS	NS
Vaidya/2002	England	RA	G allele	123	349	0.02	1.35
Tomoyose/2002	Japan	HT	G allele	143	199	0.03	

Ahmed/2001	Japan	SLE	G allele			0.003	
CT60A/G							
Ting/2016	China	Graves'	G allele	289	158	<0.001	1.63
Liu/2014*	America, Europe, and Asia	MS		12916	15455	NS	NS
Du L/2013*	China	Graves'	AA+AG				0.64
Li/2012*	Asia & Europe	RA	A allele				0.86
Kimkong/2011	Thailand	Graves'	GG	132	153	> 0.05	1.43
Chua/2010	Malaysia	SLE	Genotypes	130	130	NS	NS
Karabon/2009	Poland	MS	G allele	230	380	0.04	
Bicek/2009		AITD	AA and AG			NS	NS
Chong/2008	China	Graves'	GG	177	151	0.07	
Greve/2007	Germany Hungary & Poland	MS	Genotypes			NS	NS
Han/2006*	China	Graves'	Genotypes			NS	NS
Torres/2004	Spain	SLE	G allele	395	293	0.01	1.32
−318C/T							
Narooie/2017	Iran	Hashimoto's thyroiditis	Genotypes	82	104	NS	NS
Ting/2016	China	Graves'	Genotype	289	158	NS	NS
Liu/2014*	America, Europe and Asia	MS		12916	15455	NS	NS
Pastuszak/2013	Poland	AITDs	CT	49	69	<0.05	
Du L/2013*	China	Graves'	TT+TC				0.7
Khalilzadeh/2009	Iran	Graves'	genotypes	105	103	NS	NS
Chong/2008	China	Graves'	genotypes	177	151	NS	NS
Balbi/2007	Italy	SSc	T allele	43	93	0.03	
Tomoyose/2002	Japan	HT	genotypes	143	199	NS	NS
Hudson/2002		SLE		130	200	NS	NS
Ahmed/2001	Japan	SLE	genotypes			NS	NS

*meta-analysis, thyroid disease: autoimmune thyroid disease, Graves' disease and Hashimoto's thyroiditis, NS: no significant, SLE: systemic lupus erythematosus, Auto. D: Autoimmune disease, AITD: autoimmune thyroid disease, SSc: Systemic sclerosis, HT: Hashimoto's thyroiditis, MS: multiple sclerosis, RA: rheumatoid arthritis.

3.1. CTLA-4+49 A/G SNP (rs231775)

Studies demonstrated that CTLA-4 +49A/G is strongly associated with autoimmune diseases [63,64]. A significant association was found between the presence of CTLA-4 +49A/G, G allele and GG+GA genotypes with increased risk of Graves' disease (GD) in Chinese [65], Spanish [66], European [67] and Iranian populations [68]. However, a meta- analysis in Chinese population indicated that CTLA-4 +49A/G genotype does not correlate with Graves' disease [69]. Si et al [70] on the other hand, in a meta-analysis revealed that CTLA-4 +49A/G SNP is an important factor in increased risk of GD among Asian population.

A considerable association between G allele of CTLA-4 +49A/G SNP and increased risk of SLE has been found in Japanese and South Indian SLE patients while, many studies failed to indicate such an association in Asian and European population [71–77]. Interestingly, the meta-analysis performed by Zhai et al. revealed the protective effect of CTLA-4 +49A/G, GG+GA genotype against development of SLE disease in Asian populations [78]. Therefore, the role of CTLA-4 +49A/G, G allele in SLE trigger or development is not clear and more studies are needed to clarify the significance of CTLA-4 +49A/G polymorphism in susceptibility to SLE in different populations. The role of CTLA-4 +49A/G polymorphism as a risk factor for autoimmune disease such as Hashimoto's thyroiditis, SLE, multiple sclerosis and systemic sclerosis in various populations studied in current paper from Americas, Europe, and Asia has not been approved [79–82].

One meta-analysis and two separate case control studies revealed that G allele of CTLA-4 +49A/G is associated with increased risk of RA in Asian and European population [83–85]. The CTLA-4 +49A/G, G allele on the other hand may have a role in reducing the risk of cancer while, A allele of CTLA-4 +49A/G may increase the risk of cancer.

In a meta-analysis by Dai et al. the protective role of CTLA-4 +49A/G, G allele against breast cancer among Asian has been shown [86]. Also, the role of CTLA-4 +49A/G SNP in cervical cancer development has been investigated in meta-analysis by Liu et al. They indicated that in Asian population the presence of A allele CTLA-4 +49A/G increased risk of cervical cancer by 1.16 fold [87]. Similarly, a 1.36 fold increased risk of bone tumor was found for patients carrying CTLA-4 +49A/G, A allele in meta-analysis by Han [88].

These studies suggest that the presence of CTLA-4 +49 G allele reduces the inhibitory function of CTLA-4 on T cells. Therefore, it is logical to propose that G allele of CTLA-4 +49 A/G increases the immune system activity and decreases the risk of cancer. As the immune system alone is not enough to inhibit tumor growth, the CTLA-4 +49 G allele is not the only factor responsible for loss of immune tolerance and onset of autoimmune disorder. We suggest that G allele of CTLA-4 +49 A/G may exacerbate conditions in which the immune response against foreign antigen will increase. Consequently, in combination with other stimulus factors, which are effective in activation of autoimmune reaction this may lead to immune attack against body's cells.

Association of the AA genotype of CTLA-4 +49A/G with increased risk of renal, bladder,

cervical and hepatocellular carcinoma (HCC) has been shown in Spanish, Chinese, and Indian populations [89–91]. Cheng and coworkers have provided evidence in support of significant association between the GG genotype of CTLA-4 +49A/G gene with gastric mucosa-associated lymphoid tissue (MALT) lymphoma [92]. However, there is a lack of correlation between CTLA-4 +49 A/G SNP with increased susceptibility to cancer in various populations from Asia [93–97].

3.2. CTLA-4 CT60A/G (rs3087243)

This CTLA-4 SNP is located in 30 UTR region containing regulatory elements and can affect the mRNA stability, degradation, and nuclear transport reported by Bharti [98]. The role of CT60 A allele as a protective factor against autoimmune diseases and the CT60 G allele as a risk factor have been emphasized in several studies [99,100]. Studies performed in Chinese and Spanish population have demonstrated that G allele of CTLA-4 CT60A/G increased the risk of GD and SLE diseases [65,101].

In spite of a case control study that indicated a significant association between increased risk of acute myeloid leukemia (AML) and CTLA-4 CT60A/G, AA genotype in Spanish population, Erfani et al. have shown that AA genotype as well as A allele may have protective roles against head and neck cancer in Iranian population [102,103]. In addition, there are studies indicating lack of association of CTLA-4 CT60A/G SNP with cancer and autoimmune diseases [9,74,97]. Thus, the role of the CT60A/G polymorphism in CTLA-4 protein function and in pathogenesis of malignancies and autoimmune disorders remains unclear.

3.3. CTLA-318C/T (rs5742909)

Meta- analysis study indicated that CTLA-4 −318C/T, TT+TC strongly increased the risk of malignant cancer in Asian population [97,104]. In two case control studies performed in Asian populations, the CTLA-4 −318 C/T genotypes were in correlation with a lower risk of developing gastric mucosa-associated lymphoid tissue (MALT) lymphoma and cervical cancer [87,92]. In addition, CTLA-4 −318C/T polymorphism does not correlate with autoimmune diseases [79,105–107]. Thus, with regard to increased inhibitory function of CTLA-4 as a result of T allele substitution at position −318, it can be suggested that CTLA-4 −318C/T SNP is responsible for optimal immunological response to foreign antigens and prevention of autoimmune diseases.

4. Conclusion

The CTLA-4 SNP at position +49 in gene (A allele) may increase its inhibitory function and decrease T cell activation, which leads to weakness in immune response against cancer cells. In addition, CTLA-4 +49A/G, G allele may decrease the risk of cancer but increases the risk of autoimmune disease. The involvement of CTLA-4 +49A/G, G allele in the susceptibility to GD,

however, is unclear. The results obtained from this study concerning with CT60 A/G and −318 C/T polymorphisms effects in contributing of elucidation of CTLA-4 function were inconclusive.

Conflict of Interest

The authors declare that there is no conflict of interest to disclose.

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