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When Genetic Polymorphism Meets an Immune Checkpoint Inhibitor in Celiac Disease

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Abstract Immune checkpoint inhibitors are increasingly used as adjuvant therapy in oncology; however, they have short and long-term side effects. A major one is the surge in autoimmune diseases. The number of those conditions is continuously increasing, and recently, celiac disease was added to the list. Since celiac disease is associated with CTLA-4 polymorphism and since the disease is underdiagnosed and since the patient is at risk for various cancers, upon anti-CTRA-4 immune therapy, the loss of function of the CTLA-4 protein can predispose them to overt celiac disease. The present review highlights some potential mechanisms for CTLA-4 dysfunction, putting the patients at risk of celiac disease induction.

Keywords: *checkpoint inhibitor, immunotherapy, cancer, CTLA-4, polymorphism, celiac disease, pathophysiology*

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1. Introduction

Immune checkpoint inhibitors (ICPis) represent a recently developed anti-cancer immunotherapy based on a very conserved immune regulation that modulates over stimulation [1,2]. In fact, the immune checkpoints are pivotal cross-controls of immune tolerance and homeostasis.

Immune hyperstimulation is associated with multiple infectious, inflammatory, and autoimmune diseases (ADs) and is an important avenue to fight cancer evolvement [3,4,5]. The cross-talks between the antigen-presenting cell (APC) and the T cell are a crucial mechanism in immune homeostasis, operating through costimulatory molecules. The major players are represented by the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and its receptors, the B7 1/2 and the programmed cell death protein 1 (PD-1) and its ligands, the programmed death-ligand 1/2 (PD-L1/2) (Figure 1). When activated, those regulatory pathways modulate immune overreaction, thus, protecting the host from immune dysregulation, loss of tolerance, and autoimmunity [4]. However, this protective mechanism is a double-edged sword in cancer genesis since the cancer cells can escape the pathway designated to destroy them [5]. In reality, invasive cancers can defend themselves by stimulating those checkpoint crossroads [6,7]. When blocked by monoclonal antibodies, the ICPis disrupt those costimulatory functionalities, resulting in anti-cancer immune overreaction, for the benefit of the affected patients [8]. However, upon their introduction, toxicity and side effects are increasingly reported [9-12]. The present review will focus on the autoimmune reactions induced by those drugs, trying to explain the recently reported celiac disease-like condition post-ICPi therapy [13]. The combined contribution of CTLA-4 genetic aberrations and the anti-CTLA-4 monotherapy on CTLA-4 dysfunction in celiac disease (CD) induction is highlighted.

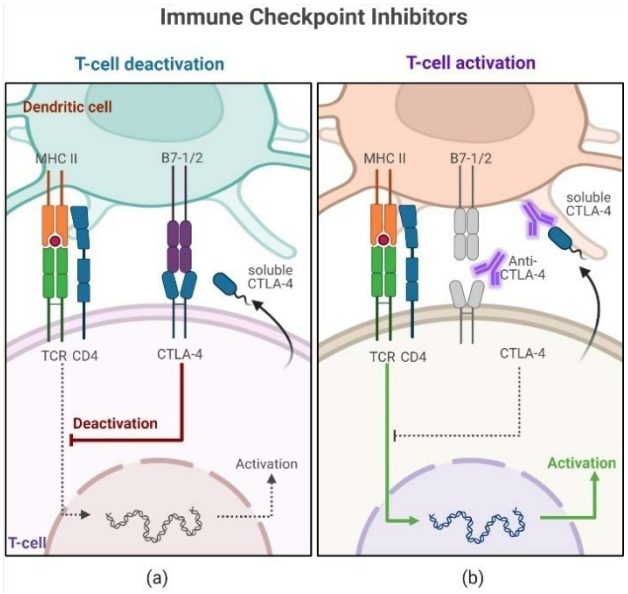

Figure 1. A schematic presentation of anti-CTLA-4 agents in action. (a) APCs, such as dendritic cells, present processed peptides to T cells on MHC molecules. Upon activation, T cells increasingly expresses CTLA-4. When it binds to B7-1/2, it initiates co-inhibition pathways that lead to T cell anergy. (b) Anti-CTLA-4 monoclonal antibodies block those inhibitory pathways resulting in effective anti-tumor T lymphocyte responses

1.1. CTLA-4 Polymorphism in Autoimmune Diseases

Being a protector of tolerance and an essential inhibitor of T-cell responses, CTLA-4 dysfunction is implicated as an auto immunogenic risk factor. In this sense, polymorphism of CTLA-4 is an important genetic marker associated with a risk of ADs development [14]. Following are some ADs associated with CTLA-4 polymorphism (Table 1)

Table 1. CTLA-4 polymorphism in various autoimmune diseases

Disease	reference
Systemic lupus erythematosus	[15]
Behçet disease	[16]
Vitiligo	[17]
Pemphigus	[18]
Myasthenia Gravis	[19]
Type 1 Diabetes mellitus	[20,21]
Graves' disease	[22]
Rheumatoid arthritis	[23]
Type 1 autoimmune hepatitis	[24]
Multiple sclerosis	[25]
Ankylosing spondylitis	[26]
Primary biliary cirrhosis	[27]
Alopecia areata	[28]
Inflammatory bowel disease	[29]
Hashimoto's thyroiditis	[30]
ANCA-associated vasculitis	[31]
Celiac disease	[32-41]

Following is a summary of polymorphic CTLA-4 and CD susceptibility.

1.2. CTLA-4 Polymorphism in Celiac Disease

A meta-analysis screened thirteen scientific reports on CTLA-4 polymorphic alleles involving 5072 CD patients, compared to 13462 controls, substantiated the association [35]. CTLA-4 alleles were studied, spanning CT60 A/G, +49 A/G, -318 C/T polymorphisms. The authors concluded that only the CT60 A/G polymorphism conferred susceptibility to CD, and no association was found with the other polymorphic alleles, at least in Europeans [35].

Over the last decades, genetic associations of several CTLA-4 polymorphic alleles conferring susceptibility to CD have been described [32-41]. Moreso, over secretion of soluble CTLA-4 in CD and some other ADs overlapping CD were reported [36,42,43,44]. However, the ability to produce the soluble form and its relationship to the various CTLA-4 polymorphic alleles is not fully understood [36] and is unknown in CD. Intriguingly, most of the CTLA-4 molecule is located intracellularly, then it is transported transmembranely to be expressed on the cell surface, capable of rapid internalization. The expressed level and the circulating soluble CTLA-4 are regulated by dynamic recycling, endocytosis, controlled neo-synthetization, and multiple genetic factors [45]. Any interference with CTLA-4 surface expression, regulation, and function might affect immune homeostasis, tolerance, and predispose autoimmunity, including CD. Finally, as a proof of concept, the anti-CTLA-4 specific ICPi are associated with CD induction [13], and even a fulminant CD case was most recently described post-ICPi therapy [46]. It seems that the CTLA-4 loss of function is a major risk factor for CD development.

2. CTLA-4 polymorphism and the Anti-CTLA-4 therapy-induced Loss of Function

Based on the crucial role of the CTLA-4 protein in tolerance induction and as a protector in ADs prevention, its dysfunction to execute its homeostatic roles is important in regulating the balance between tolerance and autoimmunity. Many processes can impact its loss of function. Table 2 summarizes those possibilities.

Table 2. A summary of potential causes for dysfunctional CTLA-4

Causes for loss of function	reference
CTLA-4 polymorphism	[14-41]
Checkpoint inhibitors usage	[5-13,46]
Dysregulation of CTLA-4 surface expression	[45]
Experimental anti-CTLA-4 antibodies	[47]

At least two of those avenues can operate in CD induction, namely, CTLA-4 polymorphism and ICPi usage.

3. Potential Mechanisms in CTLA-4 Dysfunction in CD Induction

The topic of an additive or potentiating effect of the anti-CTLA-4 ICPi and the CTLA-4 polymorphism on the protein functionality in ADs was not elucidated so far. However, several potential mechanisms can be offered. Table 3 summarizes the potential modes of action of the anti-CTLA-4 ICPi and CTLA-4 polymorphism to compromise the dysfunction of the CTLA-4 protein that might operate in CD.

Table 3. Potential mechanisms for CTLA-4 loss of function due to ICCPi and CTLA-4 polymorphism

Potential mechanisms for CTLA-4 decreased functionality	Reference
Failure to execute its moderative and tolerogenic capacity	[32-46,48,49]
Enhancement of B-cell clonality and autoantibody secretion	[50,51]
A flare-up of preexisting CD after ICPi therapy	[52,53]
CTLA-4 to small bowel antigen epitope spreading	[54,55]
Cross-presentation of shared tumor and intestinal antigens	[50]
Cross-reactive antibodies between the ICPi and intestinal antigens	[56-58]
Microbiome composition, diversity, and metabolome in CD and ICPi treated patients.	[59-61]
Local enteric expression of the immune checkpoints	[50]
ICPi toxic side effects in the duodenum	[62-64]
Duodenal pathology in primary oncological diseases, immuno and chemotherapy.	[65]
Autoimmunity due to loss of Treg homeostasis	[7,66,67]
Dysregulated intestinal surface expression of CTLA-4	[45,68]

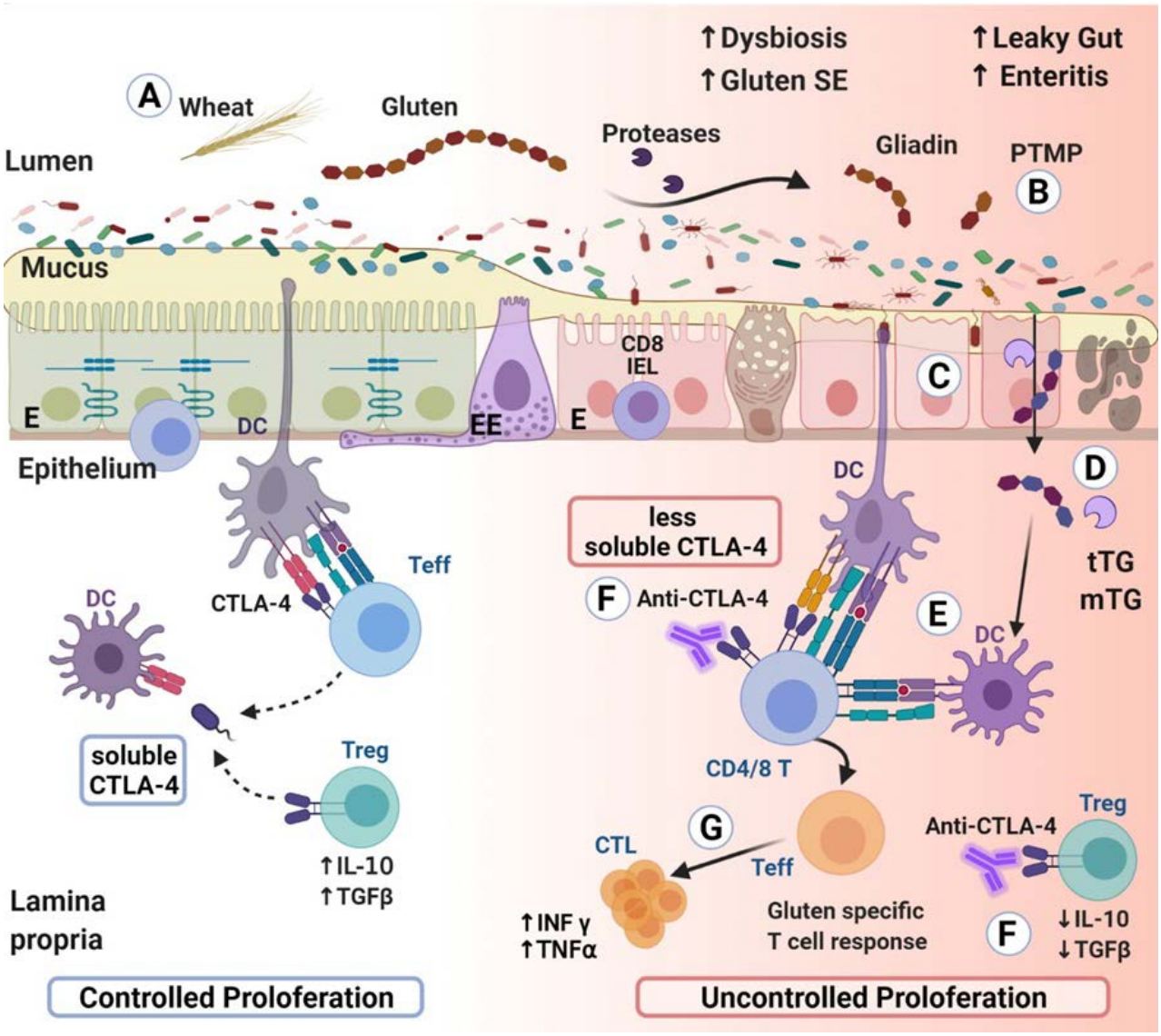

Figure 2. A schematic presentation of celiac disease induction via CTLA-4 dysfunction. (A) Gluten is ingested and digested, reaching the gut lumen as gliadin peptides. (B) Gliadins are rich in glutamine and proline, and thus are a prime substrate for deamidation and cross-linking by luminal and mucosal transglutaminases, thus, turning those naïve molecules into immunogenic ones. Transglutaminase capacity to deamidated or transamidate, results in increased post-translation modified proteins (PTMP). Luminal digestive peptidases cannot further break down those bonds, hence, inducing gut inflammation, mucus disruption, and intestinal epithelial damage. (C) Gluten increases intestinal permeability by binding to epithelial CXCR3 receptors, resulting in zonulin release. Gliadin-transglutaminase transformed peptides can potentially infiltrate through the open junctions or trans-enterocytically into the lamina propria. A breach in the epithelial barrier exposes the highly immunoreactive sub-epithelium to luminal foreign antigens, stimulating the local immune system. (D) In the lamina propria, gliadin-transglutaminase cross-linked complexes induce pro-inflammatory cytokines. (E) Two types of DC are present, sub-epithelial DCs that send protrusions into the lumen and sense the gut microbiota, and the lamina propria DCs that migrate to lymph nodes, where they present antigens and activate T cells. (F) Immune checkpoint inhibitors block co-inhibitory pathways unleashing effector T cells and depleting regulatory T cells. CTLA-4 polymorphism, such as CT60, manifest itself in less soluble CTLA-4, which leads to a more aggressive response. (G) Uncontrolled activation and proliferation of cytotoxic T lymphocytes (CTLs) further aggravate barrier perturbation, secreting IFNγ and TNFα cytokines, leading to severe intestinal damage

In summary, multiple genetic and environmental factors might induce systemic or intestinal dysfunction of the CTLA-4 molecule. Most of them are hypothetical and not fully investigated in CD-associated ICPi therapy.

4. Conclusions

Checkpoint inhibitors have various enteric side effects and are associated with ADs induction. Recently CD-like condition was associated with their usage [13]. The potential mechanism might operate in CD induction in patients with CTLA-4 polymorphic alleles, post-ICPi therapy, however, the incidence, pathophysiology, and outcome of the patients are far from being elucidated. The present review offers several potential mechanisms. It is hoped that those pathophysiological avenues will encourage the medical and scientific communities to investigate and clarify this enigma.

Abbreviations

ICPi- immune checkpoint inhibitors, CTLA-4-cytotoxic T-lymphocyte-associated protein 4, PD-1-programmed cell death protein 1, PD-L1-programmed death-ligand 1,

IRAEs-immune-related adverse events, CD-celiac disease, AD-autoimmune disease.

Author Contributions

AL- screened the literature, designed and wrote the manuscript, CB- screened the literature, edited, and revised the manuscript, designed the figure with BioRender.com permission. The two authors agreed to the published version of the manuscript.

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