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EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

Celiac Disease: Factors Involved and Immune Dysregulation as Key Event in the Pathogenesis. Review

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Received: March 06, 2017; **Published:** March 27, 2017

Abstract

Celiac Disease (CD) affects approximately 1% of the whole world population. The prevalence of CD has increased fourfold to fivefold over the past 50 years. Genetic, immunology and environmental (the intake of gluten) factors predispose to CD. The genetic condition and abnormal immune response to dietary gluten is crucial for the development of the autoimmune enteropathy. The immune dysregulation is considered as key event in the pathogenesis of CD.

In the immune dysregulation, there is loss of the immune balance with predominance of the inflammatory process on anti-inflammatory. It is makes up a network of cytokines in excess (inflammatory: Th1 phenotype) that interacting with cells in abnormal expansion. Interleukin-15(IL-15) is a regulating protein that can synergize with Interleukin-21(IL-21) which stimulates Interferon gamma (IFN-γ) production and cytolytic activity of CD8+ T and Natural Killer (NK) cells. IL-15 and IL-21 might also act in concert to disrupt local mechanisms of immune tolerance. The inhibitory regulating proteins (Interleukin-10 and Transforming Growth Factor-β-TGF-β) do not control the inflammatory response despite their biological actions and if it is maintain the inductor stimulus (gluten) in small intestine of CD patients. Also, the suppressor activity of regulatory T cells (Tregs) is significantly impaired in CD. In this disease, the persistence of the stimulus, the inadequate or non- response to inhibitor mechanisms, the maintenance and predominance of the inflammatory process with amplification of immune response, maintains the dysregulation with the consequent intestinal pathology and clinical manifestations. More studies are needed to answer the existing questions.

Keywords: *Gluten; Immune System; Cytokines, Immune Dysregulation*

Introduction

Celiac Disease (CD) affects approximately 1% of the whole world population. Since 2007, CD is considered a disease common worldwide. It is calculated that affects about 1: 100 to 1: 300 healthy [1]. The prevalence of CD has increased fourfold to fivefold over the past 50 years, and the reason for this rise is unknown, although it may relate to exposure to micro-organisms and antibiotics [2]. Genetics, immunology and environmental (the intake of gluten) factors predispose to CD. The genetic condition and abnormal immune response to dietary gluten is crucial for the development of CD [3,4].

There are three different forms of CD: latent or potential form, the silent form (asymptomatic) and the symptomatic form. The first and second forms are defined by the presence of anti-celiac antibodies, but with villous atrophy of the small intestine in the second form but not in the first. In the third form is taken into consideration the presence of anti-celiac antibodies, villous atrophy and clinical symptoms [5]. For Oligo-a-symptomatic or with atypical forms patients is difficult the diagnosis of CD [6]. In fact, the ratio between diagnosed and

undiagnosed cases was as high as 1 to 7 (the "celiac iceberg") [7]. CD can present with gastrointestinal or extraintestinal manifestations (e.g., malabsorption, dermatitis herpetiformis) [8]. Undiagnosed CD patients cannot receive opportune treatment, and will have a probability elevated for developing of secondary autoimmune disorders and malignant diseases [9].

Environmental factors (gluten), metabolome, microbiome and dysbiosis

Studies suggest that the loss of gluten tolerance does not always occur at the time of gluten introduction in the diet of genetically susceptible individuals. This can occur at any time in life as a consequence of other unknown environmental stimulus. Also, the time of development of the autoimmune process is still largely unknown [10].

The main source of gluten comes from cereals, especially wheat. Represents 80% of wheat proteins and is composed of gliadin and glutenin. Authors have demonstrated the existence of immunogenic and toxic gliadin peptides [11-14]. Some gluten peptides efficiently elicit inflammatory T-cell responses whereas others do not. The resistance to proteolytic degradation, substrate affinity to enzyme Transglutaminase 2 (TG2) and the specificity to bind to human leukocyte antigen (HLA) could be the explication. This is one of the enigmas of this disease [15].

An important element introducing is Metabolome which include a complete set of low molecular weight compounds in a cell, tissue, organ or whole organism. Serum of CD patients showed significant increases in 3-indolylacetic acid (IAA), 3-indolepropionic acid (IPA), succinic acid-SA and fumaric acid -FA. These increments can be a metabolic signal of inflammation. The liberation of metabolome, as say the investigators, can influence in the loss of gluten tolerance. Further studies are necessary to investigate the effects of metabolome on in situ immune system of CD patients [16].

The gut microbial characteristics are a consequence of HLA genotype and may contribute to the pathogenesis of CD. Strains of the Bifidobacterium genus have shown to protect against the inflammatory response and mucosal damage caused by gliadin peptides *in vitro* [17]. Specific host genetic makeup and environmental factors could promote the colonization of pathobionts and reduce symbionts, thus leading to dysbiosis. Dysbiosis may contribute to disrupting the immune homeostasis and gut integrity, favoring the beginning of CD and aggravating its pathogenesis [18].

Genetic Factors

CD is associated with genes of the major histocompatibility complex (MHC). 95% of patients are positive for HLA-DQ2 or -DQ8 [19]. The presence of HLA-DQ2 and/or DQ8 is indispensable but insufficient for the development of the disease; HLA-DQ2 genotype is also observed in 25–30% and HLA-DQ8 in 5–10% of the general population [20]. Additionally, other genes not associated with Major histocompatibility complex (MCH) class II family (non-HLA genes), are responsible for susceptibility to CD [21-23]. The high concordance rate for monozygotic twins (~80%) compared with the HLA-identical siblings (~30%) and dizygotic twins (~10%) underscores the importance of non-HLA genes in CD risk [24].

Researches [25] appoint that the vast majority of subjects who are HLA-DQ2- and HLA-DQ8-negative will never develop this disease. For others, a negative result of HLA-DQ2/DQ8 test excludes CD in 99% and a positive result points to the disease or to a predisposition to it [20,26].

Immunology factors

CD is a type IV hypersensitivity reaction mediated by antigen-specific effector T cells. It is considered an autoimmune enteropathy. This reaction takes some time to develop and gliadin antigen is absorbed by the gut and triggers the response. This type of immune reaction causes villous atrophy in small bowel and malabsorption [27].

CD is consequence from innate and adaptive immune system dysregulation [28]. Protease resistant gluten peptides transit across the intestinal epithelium via transcellular and paracellular pathways [29]. Increased epithelial permeability may be mediated by the tight-junction disruptor zonulin [30]. Native gluten peptides are deaminated by enzyme tissue Transglutaminase (tTG) and are presented by DCs in the context HLA-DQ2 and HLA-DQ8 to helper T cells which are activated and undergo differentiation to Th1 and Th2 phenotypes.

These phenotypes secrete regulating proteins or cytokines with important biological effects on other cells. The interaction of the Th2 and B lymphocytes determine the differentiation of these last on plasma cells (PC) producer of antibodies. Proinflammatory cytokines secreted by different cellular types are involved in the network, amplification of the immune response and involvement of the small intestine. These events cause disruption of the mucosa, matrix remodeling, cell death and the secretion of anti-gliadin and anti- tTG antibodies [15]. It is important to express those dendritic cells (DCs) as an antigen-presenting cell may promote the persistence of the inflammatory response by interacting with lamina propria T cells. Deregulation of DC function, either as a primary effect of gene mutations or as a consequence of defective integration with environmental cues, may result in intestinal disease [31]. Others appoint a significant reduction of the absolute number of DC, mainly the plasmacytoid subset; both in untreated and treated CD patients [32]. Distinct subpopulations of APCs in celiac disease may exert different functions in the pathogenesis [33].

Neutrophils and lymphocytes are the cells that play a major role in inflammatory processes [34]. The CD4+ T cells play an important role in tissue injury [35] and in lamina propria (LP)predominates the phenotype Th1 with production of cytokines in response to gluten stimulation [36]. Researches [37] showed that patients with CD may fail to regulate T cell response to gluten because of an impaired capacity for extra-thymic T cell receptor gene rearrangement. Th1 cells are abundant in the lamina propria and responsible for the maintenance of a suitable environment for antibody production at the duodenal mucosa and for the cytotoxic activity of intraepithelial lymphocytes (IELs) in untreated CD patients [38].

In persons with active CD, there is a marked accumulation of polarized Th-1 cells that produce large amounts of IFNγ. T-bet, a member of the T-box family of transcription factors, is present in CD4+ and CD8+ mucosal T cells in patients with CD [39,40]. An increase of TCRγδ+ IEL subset has been observed in all stages of disease: Latent CD (LCD) and Active CD (ACD) or those on a Gluten-Free Diet (GFD) and in some first-degree relatives of CD patients with HLA-DQ2 [41-43].

Treg cells have an important role in CD. Recent studies show increased numbers of circulating and mucosal CD4+Foxp3+ cells in individuals with ACD, as compared to those on a GFD [44]. However, the suppressor activity of Tregs was significantly impaired in CD patients. These results suggest that a defect in Tregs function could play a role in the pathogenesis of CD and in CD-associated autoimmunity [45]. When Th2 cells recognize antigen on B cells, helper T cells activate these cells to proliferate and differentiate into antibody-producing plasma cells. Investigators found that enzyme Transglutaminase 2 (TG2)-specific plasma cells were highly expanded in patients with active CD, representing on average 10% of Antibody-Secreting Cells (ASCs) within the duodenal mucosa. These autoantibodies presented limited somatic hypermutation in intestinal lesions of the ill patients [46].

In active CD, IELs express high levels of the activating NKG2D (NK receptor group 2, membrane D) and CD94/NKG2C receptors and 'stressed' intestinal epithelial cells express high levels of the stress-inducible MHC class I chain-related protein (MIC) molecules and non-classical MHC class I molecule HLA-E, which are the main ligands for NKG2D and CD94/NKG2C, respectively. It is important to note that in the healthy state, IELs express the inhibitory receptor CD94/NKG2A [47-49]. IL-15 plays a key role by upregulating the activating NKG2D receptor and acting as a co-stimulatory molecule, the effect being to license cytotoxic IELs with the ability to kill intestinal epithelial cells expressing the stress-induced MIC molecules. The causes of epithelial stress are not well defined [50].

For many years, studies have been conducted involving the behavior of cytokines and its influence on different cells types in pathological clinical entities. Authors indicate that the profile of mucosal effector cytokines differs between Refractory CD (RCD) and Active CD. They reported increase of IFN-γ, Interleukin -17A (IL-17A) and IL-21 transcript in ACD as well as increase of Interleukin-6(IL-6), tumoral necrosis factor-alpha (TNF-α) and IL-17A transcript in RCD. No significant increment in IL-15 transcripts was observed in both ACD and RCD, whereas IL-15 protein was increased in active CD [51]. A cytokine expressed by epithelial cells as Thymic Stromal Lymphopoietin (TSLP) is necessary to maintains of intestinal tissue and its deficiency may contribute to intestinal damage in refractory and untreated CD [52]. Interleukin-2(IL-2), soluble receptor of IL-2 (sIL-2R) and IL-6 levels have a good correlation with CD activity and can be used as reliable markers for detecting minimal transgression from GFD [53]. Researches [51] had observed a significant increment of IL-6 in RCD but no in ACD. The mechanisms of this difference are not fully understood. Interleukin-12 (IL-12) and Interleukin-18 (IL-18) is elevated

in CD and have an important suppressive effect on the induction of antigen-specific tolerance and provoke a more vigorous response on challenge. They augment the IFN-γ production, as well as active antigen-presenting dendritic cells [54]. Researchers found that TNF-α acts synergistically with IFN-γ which is the most potent inducer of TG2 expression [55].TG2 plays a critical role in the pathogenesis of CD, because it is able to deamidate glutamine residues present in toxic proteins from wheat and related cereals [56].

A study has shown increased levels of IL-15 in the intestinal epithelium and lamina propria of patients with untreated CD compared to patients in remission and healthy controls [57]. This regulating protein can synergize with IL-21 which stimulates IFN-γ production and cytolytic activity of CD8+ T cells and NK cells [58].IL-15 and IL-21 might also act in concert to disrupt local mechanisms of immune tolerance [59, 60]. Transforming Growth Factor-β (TGF-β) is inhibited by IL-15. This effect might promote and keep the intestinal inflammation [61]. Authors appoint that in the absence of the epithelial stress and increased IL-15; adaptive gluten immunity alone is insufficient to induce tissue damage [50].

IL-10 acts as immunoregulatory cytokine by interfering with antigen presentation and provokes the induction of hyporesponsive in gliadin specific T cells [62]. TGF- β is a regulating protein that has effects inhibitor on Th1 phenotype. Reports appoint that the percentage of samples expressing TGF-β mRNA from ACD patients was higher than from controls. IL-2, IFN-γ, TNF-β, IL-10, Interleukin-1β (IL-1β), and TNF-α cytokines high levels may to be relevant markers of activity in CD [63].

In conclusion, the Immune dysregulation, loss of tolerance, increased pro-inflammatory cytokines and non- suppression of the inflammatory response despite the presence of counter-regulatory mechanisms in the intestinal mucosa of celiac patients, are important events to take into consideration in CD. In the immune dysregulation, there is loss of the immune balance with predominance of the inflammatory process on anti-inflammatory. It is makes up a network of mediators or regulating proteins (cytokines) in excess that interacting with cells in abnormal expansion. Authors has been shown that these proteins participate in the regulation of the immune system in physiological entities such as pregnancy [64] and in pathologies: bacterial [65- 67], viral [68,69], parasitic [70,71], allergic [72,73], rheumatologic [74,75], neoplastic [76,77], deficiencies of Vitamin A and iron [78-80] and intolerance (autoimmune) [81,82]. In CD, the persistence of the inducing stimulus, the inadequate or non- response to inhibitor mechanisms, the maintenance and predominance of the inflammatory process with amplification of immune response, maintains the dysregulation with the consequent intestinal pathology and clinical manifestations. The immune dysregulation is considered as key event in the pathogenesis of CD.

All of the above shows that the in-depth knowledge of the pathophysiological mechanisms of the organism, especially the immune system, allows researchers to search for new therapies that improve the quality of life of CD patients. Nowadays, there is a desensitizing vaccine (NexVax2) that have three dominant gluten peptides and induces tolerogenic response in CD patients [83,84]. In the future will give answers to the existing questions.

Conflict of Interest

I have no conflict of interest.

Bibliography

1. García Novo MD., *et al*. "Prevalencia de la enfermedad celiaca en donantes de sangre de la Comunidad de Madrid". *Revista Espanola De Enfermedades Digestivas* 99.6 (2007): 337-342.

2. Rubio-Tapia A., *et al*. "Increased prevalence and mortality in undiagnosed celiac disease". Gastroenterology 137.1 (2009): 88-93.

3. Guandalini S., *et al*. "Celiac disease". *Current Opinion in Gastroenterology* 24.6 (2008): 707-712.

4. Freeman HJ., *et al*. "Recent advances in celiac disease". *World Journal of Gastroenterology* 17.18 (2011): 2259-2272.

5. Taufner G H and Afrânio Côgo Destefani. "Finding and Updates in Celiac Disease". *EC Gastroenterology and Digestive System* 1.6 (2017): 192-199.

6. Lionetti E., *et al*. "Celiac disease from a global perspective". *Best Practice and Research Clinical Gastroenterology* 29.3 (2015): 365-379.

7. Catassi C., *et al*. "The coeliac iceberg in Italy. A multicentre antigliadin antibodies screening for coeliac disease in school-age subjects". *Acta Paediatrica* 412 (1996): 29-35.

8. Schuppan, D., *et al*. "The diagnosis and treatment of celiac disease". *Deutsches Ärzteblatt International* 110.49 (2013): 835-846.

9. Yuan J., *et al*. "The tip of the "celiac iceberg" in China: a systematic review and meta-analysis". *PLoS One* 8.12 (2013): e81151.

10. Catassi C., *et al*. "Natural history of celiac disease autoimmunity in a USA cohort followed since 1974". *Annals of Medicine* 42.7 (2010): 530-538.

11. Gianfrani C., *et al*. "Celiac disease association with CD8+ T cell responses: identification of a novel gliadin-derived HLA-DQ2-restricted epitope". *Journal of Immunology* 170.5 (2003): 2719-2726.

12. Sturgess R., *et al*. "Wheat peptide challenge in coeliac disease". *Lancet* 343.8900 (1994): 758-761.

13. Maiuri L., *et al*. "In vitro activities of A-gliadin-related synthetic peptides: damaging effect on the atrophic coeliac mucosa and activation of mucosal immune response in the treated coeliac mucosa". *Scandinavian Journal of Gastroenterology* 31.3 (1996): 247-253.

14. Martucci S., *et al*. "Characterizing one of the DQ2 candidate epitopes in coeliac disease: A-gliadin 51-70 toxicity assessed using an organ culture system". *European Journal of Gastroenterology and Hepatology* 15.12 (2003): 1293-1298.

15. du Pré MF and Sollid LM. "T-cell and B-cell immunity in celiac disease". *Best Practice and Research Clinical Gastroenterology* 29.3 (2015): 413-423.

16. Sitkin SI., *et al*. "Serum metabolome by gas chromatography-mass spectrometry (GC-MS) in patients with ulcerative colitis and celiac disease". *Eksperimental'naia i klinicheskaia Gastroenterologiia* 12 (2013): 44-57.

17. Golfetto L., *et al*. "Lower bifidobacteria counts in adult patients with celiac disease on a gluten-free diet". *Arquivos de Gastroenterologia* 51.2 (2014): 139-143.

18. Cenit MC and Sanz Y. "Intestinal Microbiota and Celiac Disease: Cause, Consequence or Co-Evolution?" *Nutrients* 7.8 (2015): 6900-6923.

19. van Heel D A., *et al*. "Genetics in coeliac disease". *Best Practice and Research Clinical Gastroenterology* 19.3 (2005): 323-339.

20. Hill ID., *et al*. "Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition". *Journal of Pediatric Gastroenterology and Nutrition* 40.1 (2005): 1-19.

21. Simone R., *et al*. "A functional soluble form of CTLA-4 is present in the serum of celiac patients and correlates with mucosal injury". *International Immunology* 21.9 (2009): 1037-1045.

22. Wolters VM and Wijmenga C. "Genetic background of celiac disease and its clinical implications". *American Journal of Gastroenterology* 103.1 (2008): 190-195.

23. Romanos J., *et al*. "Six new coeliac disease loci replicated in an Italian population confirm association with celiac disease". *Journal of Medical Genetics* 46.1 (2009): 60-63.

24. Greco L., *et al*. "The first large population based twin study of coeliac disease". *Gut* 50.5 (2002): 624-628.

25. Sapone A., *et al*. "Spectrum of gluten-related disorders: consensus on new nomenclature and classification". *BMC Medicine* 10 (2012): 13.

26. Husby S., *et al*. "European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the diagnosis of coeliac disease". *Journal of Pediatric Gastroenterology and Nutrition* 54.1 (2012): 136-160.

27. Patey-Mariaud De Serre N., *et al*. "Distinction between coeliac disease and refractory sprue: a simple immunohistochemical method". *Histopathology* 37.1 (2000): 70-77.

28. Kupfer SS and Jabri B. "Celiac Disease Pathophysiology". *Gastrointestinal Endoscopy Clinics of North America* 22.4 (2012): 639-660.

29. Menard S., *et al*. "Paracellular versus transcellular intestinal permeability to gliadin peptides in active celiac disease". *American Journal of Pathology* 180.2 (2012): 608-615.

30. Fasano A., *et al*. "Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease". *Lancet* 355.9214 (2000): 1518-1519.

31. Rescigno M and Di Sabatino A. "Dendritic cells in intestinal homeostasis and disease". *Journal of Clinical Investigation* 119.9 (2009): 2441-2450.

32. Ciccocioppo R., *et al*. "Reduced number and function of peripheral dendritic cells in coeliac disease". *Clinical and Experimental Immunology* 149.3 (2007): 487-496.

33. Beitnes AC., *et al*. "Density of CD163+ CD11c+ dendritic cells increases and CD103+ dendritic cells decreases in the coeliac lesion". *Scandinavian Journal of Immunology* 74.2 (2011): 186-194.

34. Motomura T., *et al*. "Neutrophil-lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment". *Journal of Hepatology* 58.1 (2013): 58-64.

35. MacDonald TT., *et al*. "T cells orchestrate intestinal mucosal shape and integrity". *Immunology Today* 20.11 (1999): 505-510.

36. Nilsen EM., *et al*. "Gluten induces an intestinal cytokine response strongly dominated by interferon gamma in patients with celiac disease". *Gastroenterology* 115.3 (1998): 551-563.

37. Bas A., *et al*. "Aberrant extrathymic T cell receptor gene rearrangement in the small intestinal mucosa: a risk factor for coeliac disease?" *Gut* 58.2 (2009): 189-195.

38. Jabri B and Sollid LM. "Tissue-mediated control of immunopathology in coeliac disease". *Nature Reviews Immunology* 9.12 (2009): 858-870.

39. Fina D., *et al*. "Interleukin 21 contributes to the mucosal T helper cell type 1 response in CD". *Gut* 57.7 (2008): 887-892.

40. Meresse B., *et al*. "The cytokine interleukin 21: a new player in coeliac disease?" *Gut* 57.7 (2008): 879-881.

41. Maki M., *et al*. "Increase in gamma/delta T cell receptor bearing lymphocytes in normal small bowel mucosa in latent coeliac disease". *Gut* 32.11 (1991): 1412-1414.

42. Kutlu T., *et al*. "Numbers of T cell receptor (TCR) alpha beta+ but not of TcR gamma delta+ intraepithelial lymphocytes correlate with the grade of villous atrophy in coeliac patients on a long term normal diet". *Gut* 34.2 (1993): 208-214.

43. Holm K., *et al*. "Intraepithelial gamma delta T-cell-receptor lymphocytes and genetic susceptibility to coeliac disease". *Lancet* 339.8808 (1992): 1500-1503.

44. Frisullo G., *et al*. "Increased CD4+CD25+-Foxp3+ T cells in peripheral blood of celiac disease patients: correlation with dietary treatment". *Human Immunology* 70.6 (2009): 430-435.

45. Granzotto M., *et al*. "Regulatory T-cell function is impaired in celiac disease". *Digestive Diseases and Sciences* 54.7 (2009): 1513-1519.

46. Di Niro R., *et al*. "High abundance of plasma cells secreting transglutaminase 2-specific IgA autoantibodies with limited somatic hypermutation in celiac disease intestinal lesions". *Nature Medicine* 18.3 (2012): 441-445.

47. Meresse B., *et al*. "Coordinated induction by IL15 of a TCR-independent NKG2D signaling pathway converts CTL into lymphokine-activated killer cells in celiac disease". *Immunity* 21.3 (2004): 357-366.

48. Meresse B., *et al*. "Reprogramming of CTLs into natural killer-like cells in celiac disease". Journal of *Experimental Medicine* 203.5 (2006): 1343-1355.

49. Hue S., *et al*. "A direct role for NKG2D/MICA interaction in villous atrophy during celiac disease". *Immunity* 21.3 (2004): 367-377.

50. Hardy MY and Tye-Din JA. "Coeliac disease: a unique model for investigating broken tolerance in autoimmunity". *Clinical and Translational Immunology* 5.11 (2016): e112.

51. Caruso R., *et al*. "Analysis of the cytokine profile in the duodenal mucosa of refractory coeliac disease patients". *Clinical Science (London)* 126.6 (2014): 451-458.

52. Biancheri P., *et al*. "Abnormal thymic stromal lymphopoietin expression in the duodenal mucosa of patients with coeliac disease". *Gut* 65.10 (2016): 1670-1680.

53. Kapoor A., *et al*. "Serum soluble interleukin-2 receptor, interleukin-6 and tumor necrosis factor alpha as markers of celiac disease activity". *Indian Journal of Pediatrics* 80.2 (2013): 108-113.

54. Eaton AD., *et al*. "Administration of exogenous interleukin-18 and interleukin-12 prevents the induction of oral tolerance". *Immunology* 108.2 (2003): 196-203.

55. Bayardo M., *et al*. "Transglutaminase 2 expression is enhanced synergistically by interferon-γ and tumour necrosis factor-α in human small intestine". *Clinical and Experimental Immunology* 168.1 (2012): 95-104.

56. Molberg O., *et al*. "Tissue transglutaminase selectively modifies gliadin peptides that are recognized by gut-derived T cells in celiac disease". *Nature Medicine* 4.6 (1998): 713-717.

57. Di Sabatino A., *et al*. "Epithelium derived interleukin 15 regulates intraepithelial lymphocyte Th1 cytokine production, cytotoxicity, and survival in coeliac disease". *Gut* 55.4 (2006): 469-477.

58. Ebert EC. "Interleukin 21 up-regulates perforin-mediated cytotoxic activity of human intra-epithelial lymphocytes". *Immunology* 127.2 (2009): 206-215.

59. Spolski R and Leonard WJ. "Interleukin-21: basic biology and implications for cancer and autoimmunity". *Annual Review of Immunology* 26 (2008): 57-79.

60. McInnes IB and Gracie JA. "Interleukin-15: a new cytokine target for the treatment of inflammatory diseases". *Current Opinion in Pharmacology* 4.4 (2004): 392-397.

61. Wan YY and Flavell RA. "How diverse- CD4 effector Tcells and their functions". *Journal of Molecular Cell Biology* 1.1 (2009): 20-36.

62. Salvati VM., *et al*. "Recombinant human interleukin 10 suppresses gliadin dependent T cell activation in ex vivo cultured coeliac intestinal mucosa". *Gut* 54.1 (2005): 46-53.

63. Lahat N., *et al*. "Cytokine profile in coeliac disease". *Scandinavian Journal of Immunology* 49.4 (1999): 441-446.

64. Romero-Adrian TB., *et al*. "Interleukin-2 receptor serum concentrations in normal pregnancy and pre-eclampsia". *Investigación Clínica* 43.2 (2002): 73-78.

65. Romero-Adrián TB., *et al*. "Helicobacter pylori: Bacterial factors and the role of cytokines in the immune response". *Current Microbiology* 60.2 (2010): 143-155.

66. Romero-Adrián T and Leal- Montiel J. "Helicobacter pylori infection: Regulatory T cells and participation in the immune response". *Jundishapur Journal of Microbiology* 6 (2013): e5183.

67. Romero-Adrián TB., *et al*. "Role of cytokines and other factors involved in the Mycobacterium tuberculosis infection". *World Journal of Immunology* 5.1 (2015): 16-50.

68. Monsalve F., *et al*. "Serum levels of soluble CD30 molecule in hepatitis B virus infection". *Revista Medica De Chile* 129.11 (2001): 1248-1252.

69. Monsalve-De CF., *et al*. "Concentrations of cytokines, soluble interleukin-2 receptor, and soluble CD30 in sera of patients with hepatitis B virus infection during acute and convalescent phases". *Clinical and Diagnostic Laboratory Immunology* 9.6 (2002): 1372-1375.

70. Gomes JA., *et al*. "Inflammatory mediators from monocytes down-regulate cellular proliferation and enhance cytokines production in patients with polar clinical forms of Chagas disease". *Human Immunology* 75.1 (2014): 20-28.

71. Kima PE and Soong L. "Interferon gamma in leishmaniasis". *Frontiers in Immunology* 4 (2013): 156.

72. García E., *et al*. "Expression of IL-10, IL-4 and IFN-γ in active skin lesions of children with papular urticarial". *Biomedica* 31.4 (2011): 525-531.

73. Tang XQ., *et al*. "The changes in the levels of IL-6, IL-17, and IL-21 in the acute stage of childhood asthma". *Clinical Laboratory* 59.11-12 (2013): 1381-1387.

74. Brkic Z., *et al*. "T helper 17 cell cytokines and interferon type I: partners in crime in systemic lupus erythematosus?" *Arthritis Research and Therapy* 16.2 (2014): R62.

75. Shen H., *et al*. "Interleukin-4 in rheumatoid arthritis patients with interstitial lung disease: a pilot study". Indian *Journal of Medical Research* 138.6 (2013): 919-921.

76. Malekzadeh M., *et al*. "IL-17A is elevated in sera of patients with poorly differentiated ovarian papillary serous cystadenocarcinoma". *Cancer Biomark* 13.6 (2013): 417-425.

77. Souza JM., *et al*. "IL-17 and IL-22 serum cytokine levels in patients with squamous intraepithelial lesion and invasive cervical carcinoma". *European Journal of Gynaecological Oncology* 34.5 (2013): 466-468.

78. Leal JY., *et al*. "Serum values of cytokines in children with vitamin A deficiency disorders". *Investigación Clínica* 45.3 (2004): 243-256.

79. Leal JY., *et al*. "Serum levels of interferon-gamma and interleukine-10 in anemic children with vitamin A deficiency". *Archivos Latinoamericanos de Nutrición* 56.4 (2006): 329-334.

80. Leal JY., *et al*. "Serum values of interleukin-10, gamma-interferon and vitamin A in female adolescents". *Investigación Clínica* 48.3 (2007): 317-326.

81. Romero- Adrian TB., *et al*. "Celiac disease: Participation of cytokines and other factors in the immune response". *Journal of Gastrointestinal Disorders and Liver Function* 1.1 (2015): 1-9.

82. Shewry A and Hey SJ. "Do we need to worry about eating wheat?" *Nutrition Bulletin* 41.1 (2016): 6-13.

83. Levy J., *et al*. "Celiac disease: an immune dysregulation syndrome". *Current Problems in Pediatric and Adolescent Health Care* 44.11 (2014): 324-327.

84. Rossi M. "Vaccination and other antigen-specific immunomodulatory strategies in celiac disease". *Digestive Diseases* 33.2 (2015): 282-289.

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