IBD REVIEWS

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Key Role of Cytokines in Immunity of inflammatory Bowel Disease.

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Abstract

This article reviews current knowledge about the main areas of research in regards the role of cytokines implicated in the inflammatory response, onset and exacerbation of Inflammatory bowel disease (IBD).

The discussion presented in this review describes several key pro-inflammatory cytokines and anti-inflammatory cytokines, their relationship with animal models of IBD and human patients, and possible underlying mechanisms.

Keywords: Cytokine, Ulcerative Colitis, Crohn Disease, Immunity..

INTRODUCTION

Ulcerative colitis and Crohn's disease are chronically relapsing and remitting inflammatory conditions that result from chronic dysregulation of the mucosal immune system in the intestinal tract [1].

In IBD, this loss of immune tolerance toward the gut microbiota it is mediated by different molecules such as: cytokines. Several types of innate immune cells have been shown to contribute to IBD pathogenesis [2].

Elevated levels of a large variety of inflammatory mediators, including chemokines, and cytokines, have been measured in mucosal tissue samples from patients with IBD [3]. This dysregulation of the immune system with increased expression of proinflammatory cytokines are detected in active IBD patients and correlate with the severity of inflammation, indicating that these molecules may play a central role in the pathogenesis of IBD.

Studies in experimental models also indicate that IBD-related tissue damage results from dynamic intercommunications between immune and non-immune cells and that cytokines are crucial mediators of this crosstalk [4]

In this Review, we summarize the latest literature on the role of cytokines in immunity of inflammatory bowel disease.

Cytokines

Cytokines acts such as key mediators of cellular interactions in the intestine in both physiology and pathophysiology of IBD. This set of molecules are small secreted proteins released by cells have a specific effect on the interactions and communications between cells and may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action). There are both pro-inflammatory cytokines (IL-1, IL6, IL-12, IL-17, IL-23, IL-27 and anti-inflammatory cytokines (IL-19, IL-35, IL-37) [5].

Studies in vivo mouse models and human intestinal tissue have established epithelial barrier function, host defense pathways, immune regulation, and tissue repair as key pillars of intestinal homeostasis controlling the host-microbe dialogue [6].

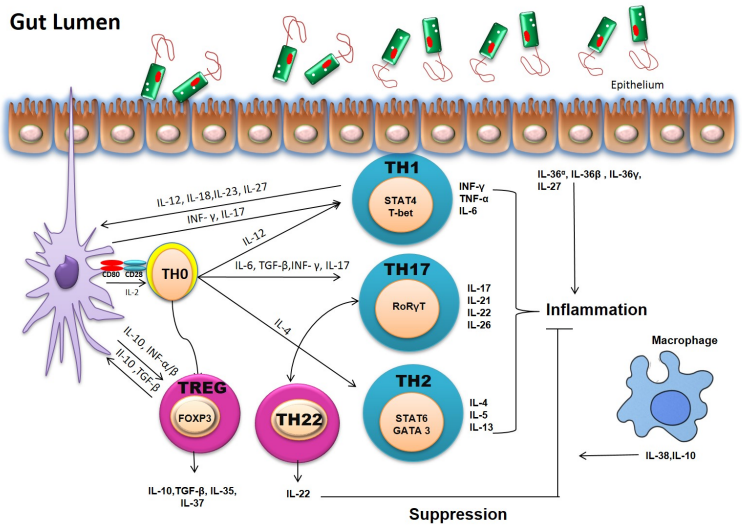
Recently have been demonstrated the involvement of dysregulation of gene expression can be linked to alterations in autophagy, UPR, ubiquitination, metabolic and immune response, pathways in the colonic mucosa of UC patients [6]. Breakdown of these pathway and the cytokine networks by which they are regulated can lead to IBD

Modulation of pro-inflammatory cytokine secretion

IL-12 drives the development of T-helper-1 (Th1) immune responses by CD4+ T-helper lymphocytes, which secrete IL-1, IL-6, interferon-gamma (IFN-γ) and TNF-α. IL-4 drives the development of a T-helper-2 (Th2) immune response by CD4+ T cells, which secrete IL-4, IL-5, IL-10, and IL-13 [7].

Thus, IL-12 induces the afore mentioned classical IFN- producing Th1 T cells, whereas IL-23 is involved in the possible maintenance and/or expansion of another polarized T-cell population, namely Th17. This latter T-cell population is characterized by the secretion of IL-17, IL-6, and TNF-These cytokines are intimately involved in innate host defense but also can play a primary role in the occurrence of tissue inflammation. Thus, IL-17 may act on cell populations to induce secretion of inflammatory chemokines that have a prompt role in rapid neutrophil recruitment. TNF-a can cause direct tissue injury, while IL-6 can enhance resistance to T cell-activated cell death (apoptosis) and survival of such inflammatory effector cells. [8-9]

Chronic inflammation in IBD is characterized by an imbalance in the production of Th1, Th2, Th17 and regulatory T subset cells Figure 1. Defects in T regulatory (Treg) cells function or in their ability to contain effector cells are related to IBD pathogenesis [10].



Th1 Polarization in IBD.

Th1 lymphocytes are critical in the cellular immune response and they play an important role in host defense systems for intracellular microbial agents and viruses. Th1 cytokines include IFNγ, IL-12 and TNF, stimulate macrophages, lymphocytes, and PMNs in the destruction of bacterial pathogens. These cytokines also help foster the development of cytotoxic lymphocytes and natural killer cells that are responsible for the cell-mediated immune response against viruses and tumor cells. [11].

Due to the central role of Th1 cells in immune system, over activation or misdirected activation also makes them key players in Th1-dominant autoimmune diseases such as: Crohn's disease, multiple sclerosis, type-1 diabetes, rheumatoid arthritis, and delayed-type hypersensitivity responses [12]

Crohn's disease is thought to be a Th1 mediated disease, mucosal T-cells from CD patients have been shown to secrete higher amounts of IFN-γ and IL-2 than from T-cells from UC patients [13-14-15]. However, data has suggested that the CD-Th1 and UC-Th2 paradigms are not so straight forward. Biopsies from both CD and UC patients have demonstrated high ex vivo levels of IFN-γ and lower levels of IL-13 have been found in UC patients as compared to CD patients [16-17]. Understanding the complicated interactions underlying the dysregulated adaptive immune response in IBD will ultimately identify novel therapeutic targets.

Th2 Polarization in IBD.

Th2 cells mediate the activation and maintenance of the humoral, or antibody-mediated, immune response against extracellular parasites, bacteria, allergens, and toxins. Th2 cells mediate these functions by producing various cytokines such as: IL-4, IL-5, IL-6, IL-9, IL-13, and IL-25 that are responsible for strong antibody production, eosinophil activation, and inhibition of several macrophage functions, thus providing phagocyte-independent protective responses [18].

Functionally, Th2 cells stimulate and recruit specialized subsets of immune cells, such as eosinophils and basophils, to the site of infection or in response to allergens. They induce mucus production and goblet cell metaplasia.

Additionally, Th2 cells are also known to be responsible for the development of asthma and other inflammatory diseases, including IBD. Interestingly, Th2 cells also produce the growth factor amphiregulin and IL-24 which have anti-tumor effects.

T cells isolated from UC biopsies do not exhibit significant production of IL-4, which has shown to be vital in the differentiation of Th2 cells and their defining cytokine [19-20] and IL4 mRNA expression in intestinal mucosa in IBD patients was undetectable [21]

Il-5 is an interleukin produced by type-2 T helper cells and mast cells. Although IL-5 is produced in these tissues, its exact contribution to UC is still unclear. In other study of cytokine transcripts in UC and CD patients' authors found IL-5, IL-13, IL-15, and IL-33 mRNA levels to be increased in UC patients [21-22]

Th17 Polarization in IBD.

Interleukin 17 (IL-17) in general induces the recruitment of immune cells to peripheral tissues, a response that requires NF-κB activation after IL-17 receptor engagement. IL-17 also leads to the induction of many pro-inflammatory factors, including TNF-α, IL-6, IL-23 and IL-1β by innate immune cells and APCs, especially dendritic cells [23-24], suggesting an important role for IL-17 in localizing and amplifying inflammation.

Furthermore, TNF-α and IL-6, which are both produced by Th17 cells, not only support Th17 cell development but also synergize with IL-17 to enhance the production of pro-inflammatory mediators [23-24].

IL-17 as well as Th17 cells have both been found to be elevated in serum and intestinal tissue of IBD patients. IL-17 was not detected in inactive patients tissue as well as other colitis [23-24-25]. The discovery and characterization of T helper 17 cells (Th17) and their signature cytokines (IL-17) represents a hallmark in T-cell immunobiology by providing a new distinctive pathway for the communication between adaptive and innate immunity [26].

Furthermore, data suggests that Th17 cell production of IL-17 and IL-23 play important roles in the pathogenesis of IBD, with DCs isolated from CD patients producing more IL-23 than UC patients [27].

In other study patients with UC, the percentage of IL-17 immunoreactive cells was higher in UC patients compared to controls. IL-17+ cells were localized mainly in mucosa, lamina propria and perivascular inflammatory infiltrates but not in goblet cells, crypt lumen or crypt branching, neither submucosa, muscularis externa and serosa. These findings suggest the important role of IL-17 in the pathogenesis of UC [23].

Regulatory Cytokine Secretion

The immunoregulatory cytokines play a critical role in the immune response of IBD. Regulatory cytokines such as IL-10, IL-35 and IL-37 are essential for maintaining the integrity and homeostasis of intestinal tissue epithelial layers. These cytokines can promote innate immune responses from tissue epithelia to limit the damage caused by viral and bacterial infections. These cytokines can also facilitate the tissue-healing process in injuries caused by inflammation [28].

Interleukin-35 (IL-35)

IL-35 is member of IL-12 family and it has anti-inflammatory/immunosuppressive properties. Li and colleagues showed that the IL-35 is not constitutively expressed in non-stimulated human tissues; IL-35 is produced by regulatory T cells (Foxp3+ Tregs) and by activated dendritic cells [29] and this novel cytokine can down-regulate Th17 cell development and inhibits autoimmune inflammation [30]

The increased immunity found in mice lacking the IL-35 production by B cells was associated with a higher activation of macrophages and inflammatory T cells, as well as an increased function of B cells as antigen-presenting cells (APCs) [31]. Moreover, Wirtz et al have demonstrated that IL-35 protects against development of T-cell–dependent colitis in mice [32].

Interleukin 37 (IL-37)

Interleukin (IL)-37 is an anti-inflammatory cytokine in the IL-1 ligand family [33]. The IL-37 plays an important role in the development and progression of inflammatory and autoimmune diseases [34]; it may be associated with the development of pediatric inflammatory bowel disease [35]. IL-37, which is normally expressed at low levels in peripheral blood mononuclear cells (PBMCs), mainly monocytes, and dendritic cells (DCs), is rapidly up-regulated in the inflammatory context [36], and therefore IL-37 conversely inhibits the production of inflammatory cytokines in PBMCs and DCs of patients with systemic lupus erythematosus. In addition, IL-37 effectively suppresses the activation of macrophage and DCs. Dendritic Cells expressing IL-37 are tolerogenic, thereby impairing activation of effector T-cell responses and inducing Treg cells. The IL-37 thus emerges as an inhibitor of adaptive immunity [37].

TH22 Polarization in IBD.

IL-22, a member of the IL-10 subfamily, is identified T-cell-derived cytokine. Expression of IL-22 is induced in several human inflammatory conditions, including IBD [38]

Sugimoto et al2 found that IL-22 gene delivery led to rapid amelioration of local intestinal inflammation in a dextran sulfate sodium-induced model of acute colitis. Expression of the IL-22 receptor is restricted to innate immune cells [39]

These results by Yamamoto et al [40] showed increased gene expression of IL-22 mRNA in rectal mucosa from patients with active UC compared to UC patients in remission and healthy controls. Interestingly, the expression of IL-22 was also significantly increased in remission UC as compared to normal controls.

Other important cytokines in IBD.

Interleukin 27

Depending on the microenvironment, IL-27 has anti and pro-inflammatory properties. As anti-inflammatory, IL-27 seems to induce a general negative feedback program that limits T and NK-T cell activity. At the onset of infection, IL-27 induces an IL-12 receptor on naïve CD4+ T cells, making them susceptible to subsequent IL-12 activity [41-42-43] [16-17-18].

The study of IL-27 performed in UC patients from a Latin American country, demonstrated the protective role of IL-27p28 (rs17855750) and IL-27EBI3 (rs428253, rs4740, and rs4905) polymorphisms in Mexican patients with UC compared to healthy controls. IL-27p28 rs17855750 polymorphism was associated with decreased risk of developing UC (OR=0.27, 95% CI: 0.06-1.13, P=0.031). Under recessive models adjusted by age and gender, the EBI3 rs428253 (OR=0.54, 95% CI: 0.29-0.99, P=0.035), rs4740 (OR=0.60, 95% CI: 0.36-1.01, P=0.046) and rs4905 (OR=0.59, 95% CI: 0.35-1.01, P=0.043) were associated with decreased risk of developing UC. Similar levels of IL-27 were observed among the genotypes of the studied polymorphisms. The authors proposed that IL-27 polymorphisms might play a protective role for the development of UC in the Mexican population [44].

IL-36 family

The IL-1 family (IL-1F) includes: the subfamily of IL-36 (IL-36Ra or IL-1F5; IL-36a or IL-1F6; IL-36b or IL-1F8; and IL-36g or IL-1F9). It has been considered one of the most important key regulators in the pathophysiology of inflammatory autoimmune diseases including: IBD, rheumatoid arthritis, and psoriasis [45-46-47]

The IL-1 family overproduction, results in inflammation, in a robust immune response that acts as first line of defense against invasive pathogenic microorganisms and damage; and when there is an aberrant immune response under appropriate genetic and environmental backgrounds in an autoimmune disease [48].

Kanda et al demonstrated that IL-36a and IL-36g contribute to gut inflammation through the induction of pro-inflammatory mediators such as IL-6 and CXCL1 [49].

Another study showed the protein expression of the presence of, IL-36 family in monocytes, CD8 T cell and plasmacytoid dendritic cell subpopulations in IBD patients [47]

IL-38

IL38/IL-1F10 is a protein that in humans is encoded by the il1f10 gene [50]. IL-38 is expressed in a range of tissues, including heart, placenta, fetal liver, skin, spleen, thymus and tonsil. IL-38 is also expressed mostly in the skin and in proliferating B cells [51]. This cytokine participates in a network of IL-1 family members to regulate adapted and innate immune responses by the inhibition of the production of T-cell cytokines (IL-17 and IL-22). IL-38 also inhibits the production of IL-8 induced by IL-36γ, thus regulating inflammatory responses [47-48-49-50-51-52].

In patients with IBD IL-38 protein expression was produced by intestinal epithelial cells, macrophages, CD8+ T cells and/or plasmacytoid dendritic cells (pDCs) was found in patients with active inflammatory bowel disease compared with non-inflamed controls [47]

CONCLUSION

In conclusion, many immunoregulatory abnormalities are described in IBD, including the ratio of proinflammatory to immunosuppressive cytokines and selective activation of T(H) lymphocyte subsets. Knowledge of the pathogenesis in IBD suggests that the ultimate goals of therapy should be to block the proinflammatory or administration of regulatory mediators to correct the dysregulated immune response.

REFERENCES

1. Lee SH, Kwon JE, Cho ML. Immunological pathogenesis of inflammatory bowel disease. Intest Res. 2018;16(1):26–42.
2. Matricon J, Barnich N, Ardid D. Immunopathogenesis of inflammatory bowel disease. Self Nonself. 2010;1(4):299–309.
3. Papadakis KA, Targan SR. Role of cytokines in the pathogenesis of inflammatory bowel disease. Annu Rev Med. 2000; 51:289-98.
4. Guan Q. A Comprehensive Review and Update on the Pathogenesis of Inflammatory Bowel Disease. J Immunol Res. 2019; 2019:7247238.
5. Zhang JM, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin. 2007;45(2):27–37.
6. Takiishi T, Fenero CIM, Câmara NOS. Intestinal barrier and gut microbiota: Shaping our immune response throughout life. Tissue Barriers. 2017;5(4):e1373208.
7. Kaiko GE, Horvat JC, Beagley KW, Hansbro PM. Immunological decision-making: how does the immune system decide to mount a helper T-cell response?. Immunology. 2008;123(3):326–338.
8. Fuss IJ. Is the Th1/Th2 paradigm of immune regulation applicable to IBD? Inflamm Bowel Dis 2008; (Suppl. 2): S110–2.
9. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature 2007; 448: 427-434
10. Fonseca-Camarillo G, Yamamoto-Furusho JK. Immunoregulatory Pathways Involved in Inflammatory Bowel Disease. Inflamm Bowel Dis. 2015;21(9):2188-93.
11. Yong-Jun Liu, et al. TSLP: An Epithelial Cell Cytokine that Regulates T Cell Differentiation by Conditioning Dendritic Cell Maturation.Annu. Rev. Immunol. 2007. 25:193–219.
12. Cho JH, Feldman M. Heterogeneity of autoimmune diseases: pathophysiologic insights from genetics and implications for new therapies. Nat Med. 2015;21(7):730#738.
13. Aggeletopoulou I, Assimakopoulos SF, Konstantakis C, Triantos C. Interleukin 12/interleukin 23 pathway: Biological basis and therapeutic effect in patients with Crohn's disease. World J Gastroenterol. 2018;24(36):4093#4103.
14. Monteleone G, Biancone L, Marasco R, Morrone G, Marasco O, Luzza F, Pallone F. Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. Gastroenterology 1997; 112: 1169-1178
15. Parronchi P, Romagnani P, Annunziato F,et al. Type 1 T-helper cell predominance and interleukin-12 expression in the gut of patients with Crohn's disease. Am J Pathol 1997; 150: 823-832
16. Rovedatti L, Kudo T, Biancheri P, Sarra M, Knowles CH, Rampton DS, Corazza GR, Monteleone G, Di Sabatino A, Macdonald TT. Differential regulation of interleukin 17 and interferon gamma production in inflammatory bowel disease. Gut. 2009;58:1629–1636.
17. Vainer B, Nielsen OH, Hendel J, Horn T, Kirman I. Colonic expression and synthesis of interleukin 13 and interleukin 15 in inflammatory bowel disease. Cytokine. 2000;12:1531–1536
18. Bamias G, Cominelli F. Role of type 2 immunity in intestinal inflammation. Curr Opin Gastroenterol.2015;31(6):471-6.
19. Karttunnen R, Breese EJ, Walker-Smith JA, MacDonald TT. Decreased mucosal interleukin-4 (IL-4) production in gut inflammation. J Clin Pathol (1994) 47(11):1015–8. doi:10.1136/jcp.47.11.1015
20. Imam T, Park S, Kaplan MH, Olson MR. Effector T Helper Cell Subsets in Inflammatory Bowel Diseases. Front Immunol. 2018;9:1212.
21. Niessner M, Volk BA. Altered Th1/Th2 cytokine profiles in the intestinal mucosa of patients with inflammatory bowel disease as assessed by quantitative reversed transcribed polymerase chain reaction (RT-PCR). Clin Exp Immunol (1995) 101(3):428–35.
22. Nemeth ZH, Bogdanovski DA, Barratt-Stopper P, Paglinco SR, Antonioli L, Rolandelli RH. Crohn's disease and ulcerative colitis show unique cytokine profiles. Cureus (2017) 9(4):e1177.
23. Fonseca-Camarillo G, Mendivil EJ, Furuzawa-Carballeda J, Yamamoto-Furusho JK. Interleukin 17 gene and protein expression are increased in patients with ulcerative colitis. Inflamm Bowel Dis. 2011 Oct;17(10): E135-6.
24. Witowski J, Ksiazek K, Jorres A. Interleukin-17: a mediator of inflammatory responses. Cell Mol Life Sci 2004; 61: 567-579
25. Fujino S, Andoh A, Bamba S, Ogawa A, Hata K, Araki Y, Bamba T, Fujiyama Y. Increased expression of interleukin 17 in inflammatory bowel disease. Gut 2003; 52: 65-70
26. Hovhannisyan Z, Treatman J, Littman DR, Mayer L. Characterization of interleukin-17-producing regulatory T cells in inflamed intestinal mucosa from patients with inflammatory bowel diseases. Gastroenterology. 2011; 140(3):957-65
27. Sakuraba A, Sato T, Kamada N, Kitazume M, Sugita A, Hibi T. Th1/Th17 immune response is induced by mesenteric lymph node dendritic cells in Crohn's disease. Gastroenterology. 2009;137:1736–1745
28. Fonseca-Camarillo G, Furuzawa-Carballeda J, Yamamoto-Furusho JK. Interleukin 35 (IL-35) and IL-37: Intestinal and peripheral expression by T and B regulatory cells in patients with Inflammatory Bowel Disease. Cytokine. 2015;75(2):389-402.
29. Li X, Mai J, Virtue A, Yin Y, Gong R, Sha X, et al. IL-35 is a Novel Responsive Anti-inflammatory Cytokine — A New System of Categorizing Anti-inflammatory Cytokines. PLoS ONE 2012; 7: e33628.
30. Kochetkova I, Golden S, Holderness K, Callis G, Pascual DW. IL-35 Stimulation of CD39+ Regulatory T Cells Confers Protection against Collagen II-Induced Arthritis via the Production of IL-10. J Immunol 2010;184: 7144-53.

31. Shen P, Roch T, Lampropoulou V, O'Connor RA, Stervbo U, Hilgenberg E, et al. IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases. Nature 2014; 507: 366-70.

32. Wirtz S, Billmeier U, Mchedlidze T, Blumberg RS, Neurath MF. Interleukin-35 Mediates Mucosal Immune Responses that Protect Against T-Cell–Dependent Colitis. Gastroenterology 2011; 141: 1875-86.

33. Kumar S, McDonnell PC, Lehr R, et al. Interleukin-1 Family of Four Novel Members of the Identification and Initial characterization of four novel members of the interleukin-1 family. J Biol Chem 2000; 275:10308-14.

34. Weidlich S, Bulau AM, Schwerd T, Althans J, Kappler R, Koletzko S, et al. Intestinal expression of the anti-inflammatory interleukin-1 homologue IL-37 in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2014; 59:e18-26.

35. Quirk S, Agrawal DK. Immunobiology of IL-37: mechanism of action and clinical perspectives. Expert Rev Clin Immunol 2014;10:1703-9.

36. Ye L, Ji L, Wen Z, Zhou Y, Hu D, Li Y, et al. IL-37 inhibits the production of inflammatory cytokines in peripheral blood mononuclear cells of patients with systemic lupus erythematosus: its correlation with disease activity. J Transl Med 2014; 12:69.

37. Chen B, Huang K, Ye L, Li Y, Zhang J, Fan X, et al. Interleukin-37 is increased in ankylosing spondylitis patients and associated with disease activity. J Transl Med 2015; 28:36-45.

38. Zenewicz LA, Yancopoulos GD, Valenzuela DM, et al. Innate and adaptive interleukin-22 protects mice from inflammatory bowel disease. Immunity. 2008;29:947–957.

39. Sugimoto K, Ogawa A, Mizoguchi E, et al.IL-22 ameliorates intestinal inflammation in a mouse model of ulcerative colitis. J Clin Invest. 2008;118:534–544.

40. Yamamoto-Furusho JK, Miranda-Pérez E, Fonseca-Camarillo G, Sánchez-Muñoz F, Dominguez-Lopez A, Barreto-Zuñiga R. Colonic epithelial upregulation of interleukin 22 (IL-22) in patients with ulcerative colitis. Inflamm Bowel Dis. 2010;16(11):1823

41. Murakami M1, Kamimura D, Hirano T. 2004. New IL-6 (gp130) family cytokine members, CLC/NNT1/BSF3 and IL-27. Growth Factors 22(2):75-77.

42. Hölscher C. 2004. The power of combinatorial immunology: IL-12 and IL-12-related dimeric cytokines in infectious diseases. Med Microbiol Immunol 193(1):1-17.

43. Matsumoto Yoh. 2013. Is interleukin-27 a real candidate for immunotherapies of multiple sclerosis? Clin Exp Neuroimmunol 4(1):7–9.

44. Yamamoto-Furusho JK, Posadas-Sánchez, Alvarez-León E, Vargas-Alarcón G. Protective role of Interleukin 27 (IL-27) gene polymorphisms in patients with ulcerative colitis. Immunol Lett. 2016; 172:79-83 Towne JE, Renshaw BR, Sims JE, et al. Interleukin-36 (IL-36) ligands require processing for full agonist (IL-36α, IL-36β, and IL-36γ) or antagonist (IL-36Ra) activity. J Biol Chem. 2011; 286 (49): 42594–602.

45. Frey S, Derer A, Messbacher ME, et al. The novel cytokine interleukin-36α is expressed in psoriatic and rheumatoid arthritis synovium. Ann Rheum Dis 2013; 72(9):1569-74.

46. Boutet MA, Bart G, Penhoat M, Amiaud J, Brulin B, Charrier C, Morel F, Lecron JC, Rolli-Derkinderen M, Bourreille A, Vigne S, Gabay C, Palmer G, Le Goff B, Blanchard F. Distinct expression of interleukin (IL)-36α, β and γ, their antagonist IL-36Ra and IL-38 in psoriasis, rheumatoid arthritis and Crohn's disease. Clin Exp Immunol. 2016;184(2):159-73.

47. Fonseca-Camarillo G, Furuzawa-Carballeda J, Iturriaga-Goyon E, Yamamoto-Furusho JK. Differential Expression of IL-36 Family Members and IL-38 by Immune and Nonimmune Cells in Patients with Active Inflammatory Bowel Disease. Biomed Res Int. 2018; 2018:5140691.

48. Milora KA, Fu H, Dubaz O, Jensen LE. Unprocessed interleukin-36α regulates psoriasis-like skin inflammation in cooperation with interleukin-1. J Invest Dermatol 2015; **135**(12):2992-3000.

49. Kanda T, Nishida A, Takahashi K, et al. Interleukin (IL)-36# and IL-36# induce proinflammatory mediators from human colonic subepithelial myofibroblasts. Front Med (Lausanne). 2015; 2:69

50. Bensen JT, Dawson PA, Mychaleckyj JC, Bowden DW."Identification of a novel human cytokine gene in the interleukin gene cluster on chromosome 2q12-14". J Interferon Cytokine Res. 2001; 21: 899–904.

51. Lin H, Ho AS, Haley-Vicente D, et al. "Cloning and characterization of IL-1HY2, a novel interleukin-1 family member," The Journal of Biological Chemistry, 2001; 276: 20597–20602.

52. Yuan X, Peng X, Li Y, Li M. Role of IL-38 and its related cytokines in inflammation. Mediators Inflamm 2015; 2015: 8079