Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

ErbB4 affects Th1/Th17 cell differentiation and promotes psoriasis progression

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ARTICLE INFO

Original paper

Article history:
Received: October 01, 2022
Accepted: November 12, 2023
Published: November 30, 2023

Keywords:

ErbB4, Th1/Th17, psoriasis, immunity

ABSTRACT

Psoriasis seriously harms people's physical and mental health. More and more people pay attention to improving the psoriasis process by immune cells. Our study alters the course of psoriasis by discovering the effect of ErbB4 on the ratio of Th1/Th17 cells. We detected the expression of ErbB4 in CD4-positive T cells in peripheral blood of clinical patients and clinical samples by qPCR and detected the expression of ErbB4 in mouse samples of the model group. ErbB4 siRNA was designed and transfected into cells. The effect of ErbB4 siRNA on Th1/Th17 cell ratio was observed by flow cytometry. ErbB4 siRNA was transfected into mice by lentivirus infection to observe its effect on psoriasis. Finally, the mechanism of ErbB4 affecting psoriasis was observed by Western Blot. According to the results, ErbB4 is highly expressed in clinical samples of psoriasis and CD4-positive T cells of patients with psoriasis. Inhibition of ErbB4 expression can reduce the proportion of Th1/Th17 cells, improve the pathogenesis of psoriasis and have therapeutic effect on psoriasis. Western Blot results showed that ErbB4 affected psoriasis through the IL23/IL17A signal axis. Our study demonstrates that ErbB4 could be a potential immune target for the treatment of psoriasis.

Doi: http://dx.doi.org/10.14715/cmb/2023.69.12.1

Introduction

Psoriasis (Psoriasis), was a common chronic inflammatory skin disease, typical skin lesions for scaly erythema or plaque (1). Psoriasis affects about 3% of the world's population. Around 125 million people suffer from psoriasis worldwide, with 150,000 new cases occurring each year. The prevalence of psoriasis in six provinces and cities in China was 0.47% in 2010. At present, there are about 6.5 million patients with psoriasis in China, and the trend is increasing year by year (2). Studies have shown that psoriasis is not only a skin disease, but also a systemic, metabolic disease. Patients with psoriasis are often complicated with hypertension, coronary heart disease, diabetes, abnormal glucose tolerance, hyperuricemia, obesity and other internal diseases (3). In 2013, the 67th General Assembly of the World Health Organization designated psoriasis as a global health problem. The exact etiology of psoriasis is not fully understood, but it may be related to genetic, environmental, immune and other factors (4). There is no completely effective treatment for psoriasis, all the current treatment measures can only achieve short-term effectiveness, and can not achieve long-term relief. The long course of psoriasis, high recurrence rate, and some courses of disease even for decades, bring greater mental pressure and economic burden to patients, and seriously affect the quality of life of patients (5). Therefore, exploring the pathogenesis of psoriasis and seeking effective treatment is a hot issue of widespread concern in society, and is also worthy of in-depth exploration and scientific research in the field of skin research. It is believed that in the context of multiple genetic abnormalities, some stimuli (such as peptides on bacterial walls) activate toll-like receptors and induce dendritic cells to produce interferon-a and TNF-a in the skin, stimulating T-cell-related adaptive immune and inflammatory responses; Thus, IL-12 and IL-23 are released to promote Th17 cell activation (6). Th17 cells promote keratinosis and eventually lead to psoriasis. The pathogenesis of psoriasis is complex, involving all aspects of innate and adaptive immunity. The cytokines mentioned above are only a few confirmed intervention sites/triggers in the pathogenesis of psoriasis (7). And these cytokines are not necessarily just part of the equation. For example, TNF-a is also involved in the Th17 keratinocyte abnormalities. Clinical studies have also proved that many other cytokines, protease and so on are involved in the pathogenesis of psoriasis (8).

Helper T cells (Th) provide complementary functions

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to other cells of the immune system, especially antigen-presenting cells (APCs) such as macrophages, dendritic cells and B cells, and play an important role in the activation and maturation of these cells (9). There are distinct subpopulations of CD4+ Th cells, including Th1, Th2, Th17, and regulatory T cells, each activated by a specific set of cytokines and transcription factors and characterized by the cytokines they secrete and the effector functions they perform (10).

ErbB (v-erb-a erythroblastic leukemia viral oncogene homolog 4) belongs to the epidermal growth factor receptor family, which consists of extracellular domains, transmembrane domains and cytoplasmic tyrosine kinase domains (11-13). In humans, the ErbB family consists of four members: ErbB1, ErbB2, ErbB3, and ErbB4. Increasing evidence suggests that ErbB4 plays a crucial role in regulating cell growth, as ErbB4 overexpression promotes cell proliferation and cell survival, while ErbB4-deficient cells exhibit decreased proliferation and cell survival (14, 15). Recently, Zhang *et al.* reported that miR-302b inhibits cancer-related inflammation by post-transcriptional regulation of ErbB4, IRF2 and CXCR4, and down-regulation of these genes leads to reduced cytokine production, suggesting that ErbB4 plays a role in inflammation (16). At the same time, ErbB4 is highly expressed in colorectal cancer cells, promoting the occurrence of colorectal cancer (17). Interestingly, in non-transformed colitis cells, inflammatory agents such as TNF-α can induce strong expression of ErbB4 through a mechanism involving NF-κB signaling (18). Both TNF-α and NF-κB play critical roles in the pathogenesis of psoriasis, and ErbB4 is highly expressed in the epidermis of the skin and influences epidermal thickness.

Therefore, we wanted to explore the regulatory relationship between ErbB4 and psoriasis through this study.

Materials and Methods

Clinical sample collection

A total of 30 psoriasis samples from patients with psoriasis and healthy individuals were used in this study. Written informed consent was obtained from all patients prior to their inclusion in this study. All tissues were stored at –80 °C before use.

Cell isolation and stimulation

Naive CD4+T cell was isolated by isolation kit from Miltenyi (130-094-131 for human naive CD4+T, 130-104-453 for mouse naive CD4+T). The isolation details followed the supplier protocol.

For Th1/Th17 cell differentiation, naive CD4+T was cultured in RPMI1640 medium (BI, Israel) contained with 1% P/S (penicillin and streptomycin) (BI, Israel) and 20% FBS (fetal bovine serum) (Gibco, NY) in an atmosphere of 5% CO2, at 37˚C. After cultured, CD3/CD28 (5μg/ml, eBioscience, 16-0037-81; 14-0289-82) functional antibody was used to stimulate the activation of Naive CD4+T cells. When CD4+T cells were activated, IFNγ (10 μg/ml, Peprotech, USA) was used to induce CD4+T cells to differentiate into Th1 cells, and TGF-β (5 ng/ml, Peprotech, USA) was used to induce CD4+T cells to differentiate into Th17 cells.

Animal model

Female BALB/c mice (6-8 weeks) were purchased from Gempharmatech Co., Ltd. The mice were raised adaptively under the same conditions. For the psoriasis-like mouse model, mice were treated with 65 mg IMQ (Imiquimod) cream (Sichuan Med-shine Pharmaceutical, H20030128) daily on their backs for 7 days. Control mice were smeared with blank cream.

ErbB4 interference

In vitro, to knock down the expression of human ErbB4, siRNA for ErbB4 (si-ErbB4: 5'-ATGCCATTTGGACA-TGTAATTGT-3') was utilized and non-specific control (si-NC: 5'-CCGUUGAAAGGCCUACCCUCA-3') were purchased from Sangon Biotech. All these sequences were transfected onto cells that grew to 60% confluence with INTERFERin (Polyplus, France). After 36 h cultured at 37˚C, 5% CO_2, cells were collected after transfection.

In vivo, to knock down the expression of mouse ErbB4, siRNA for ErbB4 (si-ErbB4: 5'-CGGGAACTAGCTG-TACGTTGTGC-3') was utilized and non-specific control (si-NC: 5'-GCUUGCGGACCAUCGAGT-3') were purchased from Sangon Biotech. All these sequences were transfected onto mice by in-vivo-JETRNA (Polyplus, France).

qPCR assay

Following the supplier's protocol, total RNA was recovered from cells by using ISOLATION TRIzol buffer® (Multi Sciences, Hangzhou), and cDNA was obtained from reverse-transcribed RNA with the RT-PCR Kit (Yeasen, China). The qRT-PCR was used PerfectStart® Sybr qPCR Mix (Vazyme, Nanjing). The expression levels were calculated by $2^{-\Delta\Delta Ct}$ assay. Primers of ErbB4 and β-actin were stated below: β-actin (human): 5'-CCATCGCCAGTTGCCGATCC-3' (F) and 5'-GC-GAGAGGAGCACAGATACCACCAA-3' (R); ErbB4 (human): 5'-GTCCAGCCCAGCGATTCTC-3' (F) and 5'-AGAGCCACTAACACGTAGCCT-3' (R); ErbB4 (mouse): 5'-CCTTCCTGCGGTCTATCCGA-3' (F) and 5'-CCAAAGTTGCCATCTTTCCTGTA-3' (R); β-actin (mouse): 5'-GTGACGTTGACATCCGTAAAGA-3' (F) and 5'-GCCGGACTCATCGTACTCC-3' (R).

Th1/Th17 ratio

Th1 and Th17 cell ratio was detected by flow cytometry (BD, C6). For human, Th1 and Th17 was marked by anti-CD4-FITC (11-0049-42), anti-IFNγ-PE (12-7319-42) and anti-IL17A-APC (17-7179-42). For mouse detection, Th1 and Th17 cells was labeled by anti-CD4-FITC (11-0041-82), anti-IFNγ-PE (12-7311-82) and anti-IL17A-APC (17-7177-81). All the antibody was obtained from eBioscience, Thermo.

H&E assay

The skin tissue of mice was fixed with 4% paraformaldehyde, dehydrated after fixed, and then embedded with paraffin. The embedded tissue was sliced (5μm) using a microtome (Leica, HistoCore BIOCUT), hematoxylin and eosin stain buffer (ServiceBio, Wuhan) were used for staining, and the sections were observed by optical microscope and preserved at room temperature.

Western blot

Whole-cell lysis was manufactured by RIPA buffer (Univ, Shanghai). 8% gel detaches protein and then was shifted to PVDF membranes (Whatman, USA). PBST (Univ, China) and 5% no-fat milk powder (CST, USA) were used to block the PVDF. Then, the PVDF was cultured for 12 h with first antibodies (Arigo, Taiwan, China), including IL23 (ARG59349), IL17A (ARG55256) and actb (ARG62346). The next day, after blocking with 2nd antibody (Abcam, China), the pattern was presented by an image capture system (Wix, USA), and the grayscale value of the target was counted by Image J.

Statistical

The average ± SD standard deviation measures data from triple repeat. Student t-test serves two cohorts. Tukey's multiple-comparison serves multiple groups. P< 0.05 means statistical difference.

Results

ErbB4 was high expression in psoriasis

In order to observe the effect of ErbB4 in psoriasis, we first need to know its expression level in psoriasis. Therefore, we collected blood samples from clinical patients for T cell enrichment and collected clinical tissue samples for detection by qPCR. In Figure 1A, the expression level of ERBB4 in peripheral blood CD4+T cells of clinical patients was higher than that of normal people. The same results were showed in Figure 1B, the expression of ErbB4 in psoriasis patients was also higher than that in normal skin. The results of qPCR showed that the expression of ErbB4 in the model group was higher than that in the normal group, no matter in CD4-positive T cells extracted from the peripheral blood of mice or in skin tissue (Figure 1C). In summary, ErbB4 is highly expressed in psoriasis.

Inhibition of ErbB4 suppressed Th1/Th17 cells differentiation

In order to understand whether ErbB4 affects the psoriasis process by influencing T cell differentiation, we tested ErbB4 levels in isolated naive CD4-positive T cells after induction stimulation. ErbB4 siRNA was transfected to interfere with ErbB4 expression and detect its effect on T cell differentiation. In Figure 2A, ErbB4 mRNA level was raised in Th17 and Th1 cells, compared to naive T cells. The transfection efficiency was determined by qPCR, the results hinted that ErbB4 siRNA played a role in inhibiting the expression of ErbB4 (Figure 2B). Crucially, flow cytometry showed that decreased expression of ErbB4 inhibited the differentiation of naive T cells into Th1/Th17 cells, and the proportion of Th1/Th17 cells was significantly reduced (Figure 2C). These results suggested that ErbB4 affects Th1/Th17 cell differentiation.

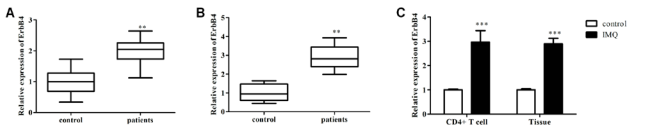

Figure 1. The expression of ErbB4 in psoriasis. A. The mRNA level of ErbB4 in CD4 positive T cells from psoriasis patients. **B.** The mRNA level of ErbB4 in skin tissues from psoriasis patients. **C.** The level of ErbB4 in IMQ-induced mice. * indicates P<0.05, ** indicates P<0.01, and *** indicates P<0.001. Data are exhibited as average ± SD.

Interference of ErbB4 alleviated the process of psoriasis

Mice models of psoriasis were constructed by using IMQ, to observe whether ErbB4 can improve psoriasis progression, we transferred ErbB4 siRNA into mice using an in vivo transfection reagent. H&E staining results showed that, compared with the blank group, the skin lesions of model group mice were serious and a large number of inflammatory cells infiltrated. The skin conditions of mice treated with ErbB4 siRNA were significantly improved, and H&E staining showed reduced inflammatory cell infiltration and improved lesions (Figure 3A). The qPCR results showed that ErbB4 was enhanced in the IMQ model group, and had declined in the IMQ+si-ERBB4 group (Figure 3B). The spleen was an important immune organ, after the dissection of mice in each group, the spleen was removed for observation, and it was found that the spleen of mice in the model group was significant-

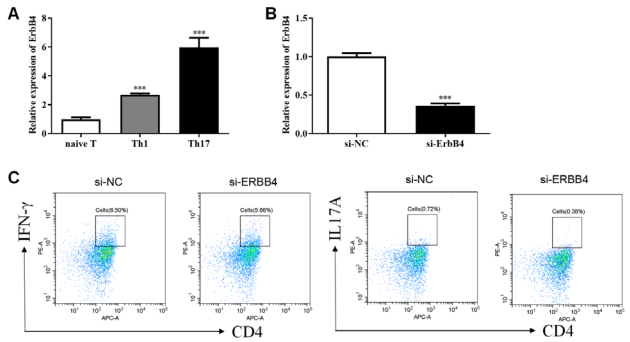

Figure 2. Effect of ErbB4 on Th1/Th17 differentiation. A. The expression of ERBB4 in different Th cells was detected by qPCR. **B.** Transfection efficiency was detected by qPCR. **C.** Flow cytometry was used to detect Th1/Th17 cell differentiation, CD4 for Helper T cell, IFNγ for Th1 cell, and IL17A for Th17 cell. * indicates P<0.05, ** indicates P<0.01, and *** indicates P<0.001. Data are exhibited as average ± SD of triple single experiments.

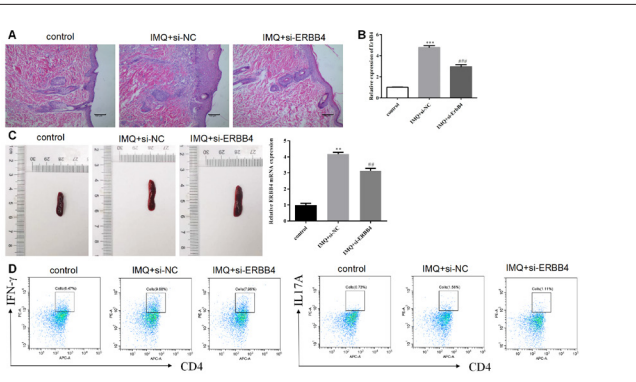

Figure 3. Impact of ErbB4 siRNA on IMQ-induced mice model. A. H&E staining was used to detect the pathological changes of skin tissue. **B.** The level of ErbB4 was calculated by qPCR. **C.** The shape of spleen was observed and photographed, and the expression of ErbB4 in CD4+T cells of spleen was detected by qPCR. **D.** Flow cytometry was used to detect Th1/Th17 cell differentiation, CD4 for Helper T cell, IFNγ for Th1 cell, and IL17A for Th17 cell. * indicates P<0.05, ** indicates P<0.01, and *** indicates P<0.001. Data are exhibited as average ± SD of triple single experiments.

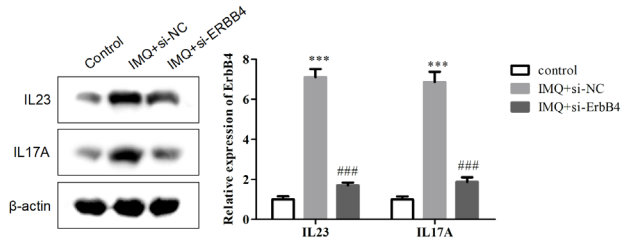

Figure 4. The Signaling mechanism of ErbB4 for psoriasis. The protein level of IL23/IL17A was determined by western blot. * indicates P<0.05, ** indicates P<0.01, and *** indicates P<0.001. Data are exhibited as average ± SD of triple single experiments.

ly enlarged, and ErbB4 siRNA could alleviate this phenomenon (Figure 3C). Flow cytometry was used to detect the Th1/Th17 ratio in the peripheral blood of mice in each group. It was found that compared with the blank group, the Th1/Th17 ratio in the model group was increased, but that in the ErbB4 siRNA group was decreased (Figure 3D). In summary, these results demonstrated that ErbB4 could alleviate the progression of psoriasis by reducing the Th1/Th17 cell ratio.

ErbB4 affected progression of psoriasis through IL23/IL17A axis

In order to explore the mechanism by which ErbB4 affects the ratio of Th1/Th17 cells in the treatment of psoriasis, IL23/IL17 was detected by Western Blot assay. From the protein results, IL23 and IL17 were raised in the model group, compared with the control group, and disturbed by ErbB4 siRNA transfection (Figure 4).

Discussion

Psoriasis is a chronic, relapsing, inflammatory and systemic immune-mediated disease induced by genetic and environmental effects (19). Due to the difficulty of treatment and the high risk of relapse, patients often suffer from it for life. It was understood that in China, the incidence of psoriasis was about 0.47%, and there were nearly 7 million patients deeply troubled by the disease, of which, nearly 60% of patients had a course of more than 10 years, more than 80% of the patients when they saw a doctor was moderate to severe disease, society was faced with a heavy burden of disease (20). Psoriasis could be cured but it was difficult to cure, conservative estimates of nearly 10 million patients, of which, more than 90% are psoriasis vulgaris, that was, the lesions mainly involve the skin, and generally did not have much impact on health (5, 21). The exact initial trigger for psoriasis was still unknown, and the cause was still being painstakingly explored. The results of the present study believed that under the premise of specific genetic background, after the effect of acquired and external environment, it leaded to skin immune dysfunction (22). For most patients with psoriasis, the impact on psychology and life was far greater than the impact on physical health, so the correct understanding and view of psoriasis was very important, active treatment and control symptoms, improve the quality of life was the key.

In our study, we found that ErbB4 was highly expressed in skin tissues and peripheral blood T cells in the psoriasis group, and inhibition of ErbB4 expression could affect the proportion of Th1/Th17 cells through the IL23/IL17 signaling axis, thus improving the therapeutic effect of psoriasis

The primary effector function of Th1 cells lies in cell-mediated immunity and inflammation, including the activation of other immune cells such as macrophages, B cells and CD8 positive cytotoxic T lymphocytes (CTLS) in cytolysis and other effector functions (23). Effector Th1 cells also secreted a large amount of IFNγ (24). In addition to further expanding the Th1 cell population, the effector Th1 cells also activated the lysate activity of macrophages by inducing more than 200 target genes. In addition to clearing intracellular infections, the Th1 response played a critical role in activating CD8+ cytotoxic T lymphocytes to target and kill tumors, in addition to enhancing CTL survival and memory (25). CD40 also promoted class switching in B cells, producing IgG2a antibodies. Th17 cytokines play a wide range of roles in inflammation and tissue protection, especially mucosal immunity. Th17 cells were essential for the maintenance of mucosal immunity, but their dysregulation was associated with the pathogenesis of autoimmune inflammation. It was their role in promoting this inflammation that first demonstrated the existence of a third subset of CD4+ T helper cells distinct from the classical Th1/Th2 model (26-28). The Th17 cytokines IL-17A and IL-17F promoted the production of pro-inflammatory cytokines in target tissues, which not only recruited innate immune cells (such as mesophils) to mediate inflammation but also further promoted Th17 activation in a positive feedback manner (29).

IL-23 was mainly produced by activated dendritic cells, macrophages and monocytes, and was a new member of the heterodimer factor family of IL-12. It was mainly composed of two subunits, IL-23p19 and IL-12/IL-23p40. IL-12/IL-23p40 was a subunit that was co-contained with IL-12. When IL-23p19 and IL-12/IL-23p40 subunits exist alone, they do not have biological functions (30). Only when the two subunits were interlinked to form homologous dimers, could they play biological functions. IL-23 played its biological function mainly by interacting with its receptors and activating downstream signaling pathways. The IL-23 receptor included the IL-12 receptor β1 (IL-12Rβ1) and two subunits of the IL-23 receptor. IL-23 mainly acted on Th17 cells, played an important role in the proliferation and stability of Th17 cells, and could promote the production of cytokines such as IL-17A, IL-17F and IL-22 in Th17 cells (31, 32).

In a word, Our study represents certification that ErbB4 modulated the psoriasis process. From this perspective, new strategies and guidelines for the diagnosis and treatment of psoriasis can be developed.

References

1. Rendon A, Schäkel K. Psoriasis Pathogenesis and Treatment. Int J Mol Sci 2019;20(6):1475. doi: 10.3390/ijms20061475. PMID: 30909615.
2. Kamiya K, Kishimoto M, Sugai J, Komine M, Ohtsuki M. Risk Factors for the Development of Psoriasis. Int J Mol Sci 2019;20(18):4347. doi: 10.3390/ijms20184347. PMID: 31491865.
3. Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker JNWN. Psoriasis. Lancet 2021;397(10281):1301-1315. doi: 10.1016/S0140-6736(20)32549-6. PMID: 33812489.
4. Griffiths CE, Barker JN. Pathogenesis and clinical features of

psoriasis. Lancet 2007;370(9583):263-271. doi: 10.1016/S0140-6736(07)61128-3. PMID: 17658397.
5. Petit RG, Cano A, Ortiz A, Espina M, Prat J, Muñoz M, Severino P, Souto EB, García ML, Pujol M, Sánchez-López E. Psoriasis: From Pathogenesis to Pharmacological and Nano-Technological-Based Therapeutics. Int J Mol Sci 2021;22(9):4983. doi: 10.3390/ijms22094983. PMID: 34067151.
6. Hoegler KM, John AM, Handler MZ, Schwartz RA. Generalized pustular psoriasis: a review and update on treatment. J Eur Acad Dermatol Venereol 2018;32(10):1645-1651. doi: 10.1111/jdv.14949. PMID: 29573491.
7. Low JM, Hyrich KL, Ciurtin C, McErlane F, Wedderburn LR; CAPS Principal Investigators. The impact of psoriasis on wellbeing and clinical outcomes in juvenile psoriatic arthritis. Rheumatology (Oxford) 2023:kead370. doi: 10.1093/rheumatology/kead370. PMID: 37467079.
8. Oji V, Luger TA. The skin in psoriasis: assessment and challenges. Clin Exp Rheumatol 2015;33(5 Suppl 93):S14-9. PMID: 26472560.
9. Zhu J. T Helper Cell Differentiation, Heterogeneity, and Plasticity. Cold Spring Harb Perspect Biol 2018;10(10):a030338. doi: 10.1101/cshperspect.a030338. PMID: 28847903.
10. Crotty S. Follicular helper CD4 T cells (TFH). Annu Rev Immunol 2011;29:621-63. doi: 10.1146/annurev-immunol-031210-101400. PMID: 21314428.
11. Segers VFM, Dugaucquier L, Feyen E, Shakeri H, De Keulenaer GW. The role of ErbB4 in cancer. Cell Oncol (Dordr) 2020;43(3):335-352. doi: 10.1007/s13402-020-00499-4. PMID: 32219702.
12. Lucas LM, Dwivedi V, Senfeld JI, Cullum RL, Mill CP, Piazza JT, Bryant IN, Cook LJ, Miller ST, Lott JH 4th, Kelley CM, Knerr EL, Markham JA, Kaufmann DP, Jacobi MA, Shen J, Riese DJ 2nd. The Yin and Yang of ERBB4: Tumor Suppressor and Oncoprotein. Pharmacol Rev 2022;74(1):18-47. doi: 10.1124/pharmrev.121.000381. PMID: 34987087.
13. El-Gamal MI, Mewafi NH, Abdelmotteleb NE, Emara MA, Tarazi H, Sbenati RM, Madkour MM, Zaraei SO, Shahin AI, Anbar HS. A Review of HER4 (ErbB4) Kinase, Its Impact on Cancer, and Its Inhibitors. Molecules 2021;26(23):7376. doi: 10.3390/molecules26237376. PMID: 34885957.
14. Roskoski R Jr. The ErbB/HER family of protein-tyrosine kinases and cancer. Pharmacol Res 2014;79:34-74. doi: 10.1016/j.phrs.2013.11.002. PMID: 24269963.
15. Estupiñán HY, Berglöf A, Zain R, Smith CIE. Comparative Analysis of BTK Inhibitors and Mechanisms Underlying Adverse Effects. Front Cell Dev Biol 2021;9:630942. doi: 10.3389/fcell.2021.630942. PMID: 33777941.
16. Zhang M, Zhang L, Cui M, Ye W, Zhang P, Zhou S, Wang J. miR-302b inhibits cancer-related inflammation by targeting ERBB4, IRF2 and CXCR4 in esophageal cancer. Oncotarget 2017;8(30):49053-49063. doi: 10.18632/oncotarget.17041. PMID: 28467773.
17. Frey MR, Edelblum KL, Mullane MT, Liang D, Polk DB. The ErbB4 growth factor receptor is required for colon epithelial cell survival in the presence of TNF. Gastroenterology 2009;136(1):217-26. doi: 10.1053/j.gastro.2008.09.023. PMID: 18973758.
18. Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. JAMA 2020;323(19):1945-1960. doi: 10.1001/jama.2020.4006. PMID: 32427307.
19. Korman NJ. Management of psoriasis as a systemic disease: what is the evidence? Br J Dermatol 2020;182(4):840-848. doi: 10.1111/bjd.18245. PMID: 31225638.
20. Hugh JM, Weinberg JM. Update on the pathophysiology of psoriasis. Cutis 2018;102(5s):6-12. PMID: 30566550
21. Bocheńska K, Smolińska E, Moskot M, Jakóbkiewicz-Banecka J, Gabig-Cimińska M. Models in the Research Process of Psoriasis. Int J Mol Sci 2017;18(12):2514. doi: 10.3390/ijms18122514. PMID: 291867.
22. Ji C, Wang H, Bao C, Zhang L, Ruan S, Zhang J, Gong T, Cheng B. Challenge of Nail Psoriasis: An Update Review. Clin Rev Allergy Immunol 2021;61(3):377-402. doi: 10.1007/s12016-021-08896-9. PMID: 34478047.
23. Ruterbusch M, Pruner KB, Shehata L, Pepper M. In Vivo CD4+ T Cell Differentiation and Function: Revisiting the Th1/Th2 Paradigm. Annu Rev Immunol 2020;38:705-725. doi: 10.1146/annurev-immunol-103019-085803. PMID: 32340571.
24. Zhang Y, Zhang Y, Gu W, Sun B. TH1/TH2 cell differentiation and molecular signals. Adv Exp Med Biol 2014;841:15-44. doi: 10.1007/978-94-017-9487-9_2. PMID: 25261203.
25. Jiang H, Fu D, Bidgoli A, Paczesny S. T Cell Subsets in Graft Versus Host Disease and Graft Versus Tumor. Front Immunol 2021;12:761448. doi: 10.3389/fimmu.2021.761448. PMID: 34675938.
26. Seyed N, Rafati S. Th1 concomitant immune response mediated by IFN-γ protects against sand fly delivered Leishmania infection: Implications for vaccine design. Cytokine 2021;147:155247. doi: 10.1016/j.cyto.2020.155247. PMID: 32873468.
27. Yasuda K, Takeuchi Y, Hirota K. The pathogenicity of Th17 cells in autoimmune diseases. Semin Immunopathol 2019;41(3):283-297. doi: 10.1007/s00281-019-00733-8. PMID: 30891627.
28. Yan JB, Luo MM, Chen ZY, He BH. The Function and Role of the Th17/Treg Cell Balance in Inflammatory Bowel Disease. J Immunol Res 2020;2020:8813558. doi: 10.1155/2020/8813558. PMID: 33381606.
29. Miossec P, Kolls JK. Targeting IL-17 and TH17 cells in chronic inflammation. Nat Rev Drug Discov 2012;11(10):763-76. doi: 10.1038/nrd3794. PMID: 23023676.
30. Schmitt H, Neurath MF, Atreya R. Role of the IL23/IL17 Pathway in Crohn's Disease. Front Immunol 2021;12:622934. doi: 10.3389/fimmu.2021.622934. PMID: 33859636.
31. Wang R, Maksymowych WP. Targeting the Interleukin-23/Interleukin-17 Inflammatory Pathway: Successes and Failures in the Treatment of Axial Spondyloarthritis. Front Immunol 2021;12:715510. doi: 10.3389/fimmu.2021.715510. PMID: 34539646.
32. Bunte K, Beikler T. Th17 Cells and the IL-23/IL-17 Axis in the Pathogenesis of Periodontitis and Immune-Mediated Inflammatory Diseases. Int J Mol Sci 2019;20(14):3394. doi: 10.3390/ijms20143394. PMID: 31295952.