The Egyptian Journal of Hospital Medicine (July 2022) Vol. 88, Page 2736-2741

Interleukin-23 and its Receptor Expression (IL-23R) in Psoriatic and Psoriatic Arthritis Patients

Mohamed Saad Serria[*1], Eman Hamza[1,4], Nessma A. Nosser[2], Marwa Zohdy[3], Fatma Azzahraa Hisham[1]
Departments of [1]Medical Biochemistry and Molecular Biology, [2]Clinical Pathology, and [3]Dermatology, Venereology and Andrology, Faculty of Medicine, Mansoura University, Mansoura, Egypt
Department of [4]Biochemistry and Molecular Biology, Horus University, Damietta, Egypt
***Corresponding author:** Mohamed Saad Serria, **Mobile:** (+20)01015980585, **E-mail:** sorriaeg@mans.edu.eg

ABSTRACT

Background: Psoriasis (Ps) is a systemic autoimmune disorder that develops under the influence of environmental factors in a genetically susceptible person. The IL-23/IL-17 axis is the primary signaling pathway for cellular and molecular alterations in Ps. **Objective:** This study aimed to investigate the serum levels of interleukin-23 (IL-23) and its receptor (IL-23R) expression in patients with Ps and psoriatic arthritis (PsA), as well as to evaluate the possibility of using (IL-23R) in blood as a helpful marker for diagnosis of psoriasis and susceptibility to psoriatic arthritis. **Patients and Methods:** Medical data and clinical evaluations were done, and blood samples from patients and control groups were collected. Serum IL-23 concentration was measured using enzyme-linked immunosorbent assay (ELISA) and the expression of IL-23R in human peripheral blood mononuclear cells (PBMCs) was determined using western blotting. **Results:** Serum IL-23 concentration was significantly higher among Ps cases than in controls and it was significantly different between Ps and PsA groups. The protein expression of IL-23R was significantly greater in the Ps group than in the control group, with no significant difference between Ps and PsA groups. The receiver operating characteristics curve (ROC) curve showed a diagnostic value for the increased blood IL-23R with a sensitivity of 83.3% and a specificity of 73.3% for psoriasis. Also, ROC curve showed a diagnostic value for the increased blood IL-23 with a sensitivity of 80% and a specificity of 73.3% for the diagnosis of psoriasis. **Conclusion:** Serum IL-23 and its receptor expression measurements are helpful tools in the diagnosis of Ps as well as in the prediction of PsA. We demonstrated that there is a link between IL-23 and IL-23R and the risk of Ps in addition to PsA, with evidence that the expression of IL-23R is linked to a significantly greater risk of psoriasis.

Keywords: IL-23, IL-23R, Expression, Psoriasis, Psoriatic arthritis.

INTRODUCTION

Psoriasis is one of the most prevalent autoimmune, inflammatory and proliferative dermatosis which involves 2%-3% of the world's population and is frequently associated with other comorbidities, including inflammatory bowel disease and arthritis. Classical plaque psoriasis has focal inflamed, red and raised plaques due to overgrowth of epithelial cells [(1)].

Other clinical subtypes include (guttate, pustular, and erythrodermic). Early onset Psoriasis accounts for 75% of cases and occurs before the age of 40[(2)]. Psoriasis is caused by the imbalance between innate and adaptive immune components of skin cells due to disturbance in cytokines [(3)]. The skin inflammation increases the serum and local concentrations of many cytokines as TNF-α, IFN-γ, IL-1, IL-23 and IL-17. Psoriasis was thought to be a Th1-driven disease because of the increased Th1-cell pro-inflammatory cytokines in relation to Th2-type cytokines [(4)].

It was demonstrated that mice received IL-23 minicircle DNA in vivo developed psoriasis and arthritis [(5)]. Furthermore, the interference with IL-23 signalling pathway by neutralizing antibodies showed effectiveness against several inflammatory conditions including psoriasis. In addition, intradermal injections of IL-23 in mice result in a psoriasis-like disease with increased transcription of IL-23/Th17-related genes. Therefore, IL-23 and Th17 axis might have an important role in Ps pathogenesis. It was revealed by some studies that increased systemic level of IL-23 is not an absolute necessity for skin or joint disease development as augmented by the transgenic *K23* mice, (mouse model of Ps and PsA caused by selective and conditional skin expression of IL-23) [(6)]. Thus, factors induced by IL-23 in the skin (IL-17 and IL-22) can be pathogenic and initiate joint disease [(7)].

Interleukin-23 belongs to IL-12 cytokine family and is formed of two subunits; p19 is a unique for IL-23 and p40 which is also a component of IL-12. It binds to a receptor complex that consists of IL-23R and the IL-12 receptor β1[(8)]. IL-23 is released by keratinocyte and activated antigen-presenting cells (APCs), and its action is mainly mediated by the production of inflammatory mediators [(9)].

There is accumulating evidence that IL-23 has a role in maintaining the immune responses through controlling the function of T-cell memory and affecting the proliferation and survival of IL- 17- producing T helper 17 (Th17) cells. Many data revealed that T lymphocyte expresses IL-23R and respond to IL-23 by releasing IL-17 and IL-22[(10)]. IL-23 stimulates IL-17 synthesis by natural killer cells and neutrophils to control the acute infections and by Th17 cells leading to the formation of autoreactive IL-17-producing T-lymphocytes that provoke chronic autoimmune inflammatory process (adaptive)[(11)]. Thus IL-23 links the innate with adaptive immunity. More than 160 unique genes were activated by IL-23, including new DNA-binding proteins and a large number of expression sequence tags that are still of unknown functions. Also, IL-23 promotes upregulation of the matrix

Received: 09/01/2022
Accepted: 07/03/2022

metalloprotease MMP9 and stimulates antigen presentation by dendritic cells [12].

Under the stimulation of various cytokines, naïve CD4+T cells undergo differentiation into Th1, Th2, Th17, or T follicle helper cells. The Th17 cell has a significant role in the pathogenic process of Ps as it releases IL-17A, IL-17F, IL-22, IL-21, TNF-α, and interferon-γ [13]. Th17 cell differentiation is regulated by reciprocal association with CD4+ regulatory cells (Tregs) whose key function is to inhibit T-cell response against self and foreign antigens [14]. Naive CD4+ T cells in existence of TGF-β1 mature to Foxp3 + (Tregs) cells whereas in the existence of both IL-6 and TGF-β1, mature to ROR- γδ + Th17 cells which when further exposed to IL-23 become pathogenic Th17 cells [15]. So, manipulation of the differentiation pathway in between both cells may result in novel therapeutic targets in chronic inflammatory diseases. Cytokines produced by Th17 recruit neutrophils and monocytes to the lesion site, which in turn produces multiple inflammatory factors that mediate the pathogenesis of psoriasis [16].

The *IL-23R* gene exists on chromosome 1 (1p31). IL-23R is a type I cytokine receptor that pairs with the receptor molecule IL-12R β1, to confer IL-23 responsiveness probably through activation of the Jak-Stat signalling cascade on cells that express both subunits [17]. IL-23R mRNA transcript is approximately 2.9-kb. IL-23R cDNA encodes a 629 aa type I transmembrane protein. IL-23R is a key determinant of the pathogenicity and of autoimmunity of Th17 cells in general [18]. IL-23R has a significant role in the proliferation and survival of Th17 cells that are important for the host defence against bacteria, fungi, and viruses. *IL-23R* gene polymorphisms might affect IL-23 responses. Dysregulation of IL-23/IL-17 axis, causes a break in self-tolerance to tissues and antigens, resulting in severe autoimmune responses [19].

In current study we aimed to corelate the level of serum IL-23 and its receptor expression in blood with the pathogenesis and/or the diagnosis of Ps and susceptibility to PsA.

PATIENTS AND METHODS

Patients

Sixty cases were enrolled in a case control study. All cases were obtained from patients attending Mansoura university hospital, dermatology clinic; thirty were diagnosed with PsA and thirty had Ps. In addition, thirty persons of age and sex-matched healthy volunteers were used as controls. Medical and clinical evaluations were done. Pregnant women or women on hormonal contraception and subjects with immune-mediated comorbidities and systemic disease were excluded from the start. Psoriasis area and severity index (PASI) scores were recorded to quantify Ps severity in each patient.

Ethical consent:

Signed consents were obtained from all subjects. The research protocol obtained its approval from University of Mansoura (Code number: R.21.10.1501). This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Preparation of samples

Overall, 10 ml of venous blood samples were obtained from all subjects by venepuncture under aseptic conditions. 5 ml were poured into serum separator tubes. After clotting, centrifugation at 2000g for 10 minutes was performed, and the sera underwent separation and storage at −20°C until used for ELISA. The remaining 5 ml blood samples were withdrawn into EDTA-containing tubes and immediately placed on ice; isolation of white blood cells (WBCs) from all these samples using RBCs lysis buffer, then used for Determination of IL-23R protein by western blotting.

Detection of serum IL-23 concentration by ELISA

Serum IL-23 was quantitated by ELISA method using a commercially available Human IL-23 ELISA Kit (Biolegend, San Diego, CA, USA). Measuring absorbance at a wavelength of A450 nm.

Detection of blood IL-23R protein by western blotting

Total protein from cells underwent extraction utilizing the QIAzol Reagent (Qiagen, Germany Cat. No.79306), based on the manufacturer's specification and measured by the BCA assay (Bosterbio, Canada). Separation of pre-stained protein molecular weight marker (Thermo Scientific, USA) and equal amounts of proteins (10 mg) was performed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (10%). Then transferred to nitrocellulose membrane (Abcam, USA) utilizing Eco-Line Biometra apparatus (Gottingen, Germany), incubated in 5% non-fat milk (a blocking agent), over 60 minutes at 37°C. The membranes underwent incubation overnight at 4°C with anti-human IL-23R unconjugated primary antibody (Santa Cruz Biotechnology, USA, Cat. No. sc-293485), and a rabbit antihuman glyceraldehyde 3-phosphate dehydrogenase (GAPDH) polyclonal antibody as internal control (Santa Cruz Biotechnology, USA, Cat. No. sc-25778) in blocking buffer. After incubation with Goat anti-rabbit IgG antibody conjugated to horseradish peroxidase (HRP) (Santa Cruz Biotechnology, USA, Cat. No. sc-2030) at 37°C for 120 minutes, bound proteins were visualized utilizing colorimetric immuno-detection by 1-Step TMB-Blotting (Thermo Scientific, US).

Membrane bands were digitally photographed and the resulted photographs were analysed using ImageJ software for calculation of the relative protein concentrations depending upon the ratio between peak areas of the IL-23R proteins in relation to GAPDH.

Statistical analysis

Data were analyzed by the Statistical Package of the Social Sciences (SPSS) program for Windows (version 21). At first, one-sample Kolmogorov-Smirnov test was utilized to test for normality of data. Qualitative data were represented as numbers and percent. Correlation between categorical variables was tested utilizing Chi-square test whereas Fischer exact test was applied when expected cell count less than 5. Continuous variables were represented as means ± SDs (standard deviations) for normally distributed data and medians (min-max) for non-normal data. The 2 groups underwent comparison by Student t test for normal data and Mann Whitney test for non-normal data. Sensitivity and specificity at different cut off points were tested by ROC curve. $P< 0.05$ was considered significant.

RESULTS

Demographics and selected clinical data of studied groups

The patient's medical history, PASI score[20] was recorded. Ninety persons (40 males and 50 females) were enrolled in this study in three groups, with 30 individuals for each group (PsA, Ps and control). The female: male ratio was 17:13 for PsA, 13:17 in Ps, and 20:10 in control groups.

The mean patient age in years was (47.47 ± 7.37) for PsA, (46.53 ± 9.9) for Ps and (45.1±10.06) for the control group. The mean BMI is (35.8±4.33 kg/m2) for PsA and (33.80±2.97 kg/m2) for Ps; both groups are overweight. There is a highly significant difference in BMI in PsA and Ps ($p\leq0.001$) when compared with the BMI of the control group (30.13±4.40 kg/m2). Also, there was a significant difference in BMI ($p=0.042$) between PsA and Ps. The duration of the disease varied from (0.5-25 years) in PsA and (0.5- 7 years) in Ps. Although patients with PsA had more frequent rheumatoid factor (RF) (13.3%) than patients with Ps (3.3%), the difference was insignificant ($P=0.353$), and the RF value was nearly the same (Table 1).

Table (1): Demographics and some clinical data of the study groups

	Psoriatic arthritis (n=30)	Psoriasis (n=30)	Control (n=30)	Test of significance		
				P1	*P2*	*P3*
Age (years) Mean ± SD	47.47±7.37	46.53±9.9	45.10±10.06	t=1.04 $p=0.303$	t=0.566 $p=0.58$	t=0.414 $p=0.680$
Sex Male Female	 13 (43.3%) 17 (56.7%)	 17 (56.7%) 13 (43.3%)	 10 (33.3%) 20 (66.7%)	$\chi^2=0.635$ $P=0.426$	$\chi^2=3.03$ $P=0.069$	$\chi^2=1.06$ $P=0.302$
BMI Mean ± SD	35.8±4.33	33.80±2.97	30.13±4.40	t=5.02 $p\leq0.001$*	t=3.78 $p\leq0.001$*	t=2.08 $p=0.042$*
Duration of Ps. Median (Min-Max)	4 (0.5-25)	3 (0.5-7)	-	-	-	Z=1.12 $p=0.263$
PASI Score Mean ± SD	17.10±2.11	17.50±1.94	-	-	-	t=0.764 0.448
No of swollen / Tender Joint Median (Min-Max)	4 (1-35)	-	-	-	-	-
Rheumatoid factor (RF): Positive Negative	 4 (13.3%) 26 (86.7%)	 1 (3.3%) 29(96.7%)	-	-	-	FET $p=0.353$
RF value Mean ± SD	11.05±3.75	11.20±0.0	-	-	-	t=1.4 $p=0.167$

P1: Comparison between psoriatic arthritis and control groups, *P2*: Comparison between psoriasis and control groups, *p3*: Comparison between psoriatic arthritis and psoriasis groups. Z: Mann Whitney test, FET: Fischer exact test. χ^2: Chi square test, t: student t test, *significant *P*

Selected biochemical parameters of studied groups

As demonstrated in table (2) the biochemical parameter of inflammation investigated (CRP) and it was significantly higher in PsA and Ps ($p\leq0.001$) in comparison to controls. Also, the mean serum uric acid concentration was significantly greater ($p \leq0.001$) among PsA cases and insignificant among Ps cases when compared with controls ($p=0.086$). Also, a significant difference existed in uric acid levels between PsA and Ps patients ($p\leq0.001$). Again, in table 2, the serum concentrations of IL-23 were significantly greater among Ps cases (Median (Min-Max) 25.36 pgm/ml (16.45-41.31) and PsA (Median (Min-Max) 35.15 pgm/ml (18.71-43.73) than in control subjects (Median (Min-Max) 3.12 pgm/ml (1.08-13.43). Also, a significant difference existed in IL-23 level between PsA and Ps patients ($p=0.006$).

The presence of IL-23R in PBMCs was quantified by western blotting (Figure 1). Western blotting demonstrated increased IL-23R protein expression in both Ps and PsA groups, as compared with the control. Protein bands were digitized, and the net band intensities were recorded and expressed as pixels.

Figure (1): Blotting membrane for IL-23R expression in human PBMCs. MW of IL-23R is 55 kDa and of GAPDH is 37 kDa. GAPDH: glyceraldehyde 3-phosphate dehydrogenase (GAPDH). IL-23R: interleukin-23 receptor.

Finally, (IL-23R/GAPDH ratio) was significantly higher in PsA and in Ps ($p \leq 0.0001$, $p \leq 0.001$). The median band intensities with the minimum and maximum intensities (PsA 0.31 (0.04-0.86), Ps 0.31 (0-0.66) (Table 2). The protein expressions of IL-23R were significantly greater among patients than in control subjects but non-significant difference exists between Ps and PsA groups. In contrast, no significant difference was observed for the levels of IL-23 or its receptor according to the disease severity or duration. Data were processed by nonparametric Mann-Whitney tests.

Table (2): Biochemical parameters of studied groups

	Psoriatic arthritis (n=30)	Psoriasis (n=30)	Control (n=30)	Test of significance		
				P1	*P2*	*P3*
Uric Acid mg/dL Mean ± SD	8.73±2.10	5.78±1.90	5.07±1.15	t=7.76 $p \leq 0.001$*	t=1.74 $p=0.086$	t=5.04 $p \leq 0.001$*
CRP ng/mL Mean± SD	10.31±2.15	9.50±1.73	2.07±0.66	$p \leq 0.001$*	$p \leq 0.001$*	$p=0.526$
IL-23/pgm/ml Mean ± SD	35.15±7.15	25.36 ±5.12	3.12 ±0.62	Z=6.65 $p \leq 0.001$*	Z=6.59 $p \leq 0.001$*	Z=2.74 $p=0.006$*
IL-23R relative quantification (IL-23R/GAPDH ratio) Mean ± SD	0.31 ±0.05	0.31 ±0.04	0.0 ±0.0	Z=5.06 $p \leq 0.001$*	Z=4.06 $p \leq 0.001$*	Z=0.799 $p=0.425$

Z: Mann Whitney test, t: student t test, *significant *P*

ROC curve analysis of IL-23 and IL-23R/GAPDH ratio for diagnosis of psoriasis

ROC curve analyses were used to define the diagnostic profile of IL-23 and its receptor. Results demonstrated an AUC of 0.79 for IL-23 in the diagnosis of psoriasis with 80% sensitivity and 73% specificity, whereas the best IL-23 cut-off value was > 0.122. The area under the curve (AUC) of IL-23R/GAPDH ratio was 0.873 for the diagnosis of psoriasis with a sensitivity of 83.3%, a specificity of 73.3% and the best IL-23R/GAPDH cut-off value was > 0.123 (Figure 2).

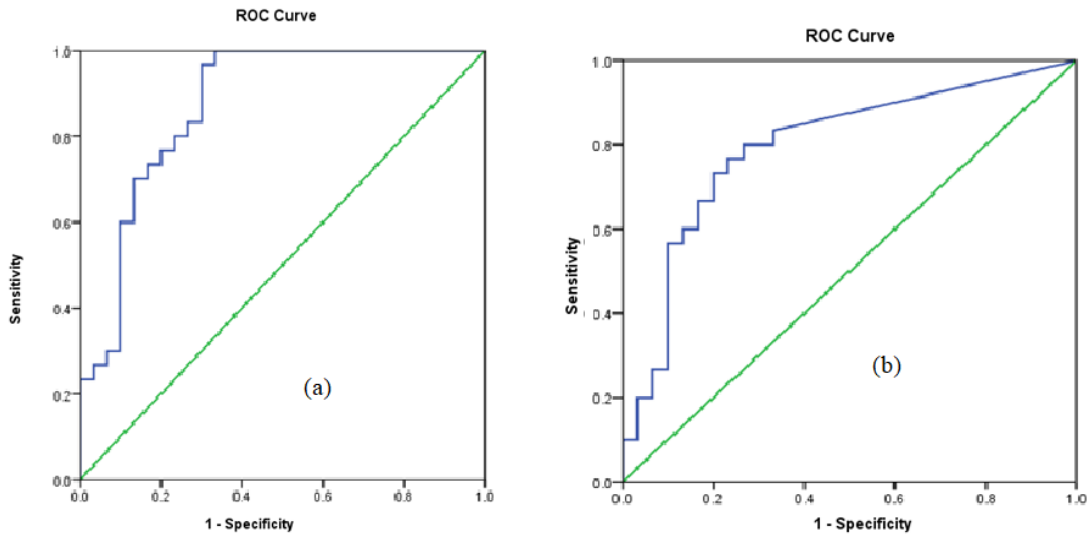

Figure (2): ROC curve for diagnosis of psoriasis using IL-23R/GAPDH ratio (a) and (b) IL-23

DISCUSSION

The pathologic consequences of increased IL-23 signalling have been associated with its capacity to enhance inflammatory mediators' synthesis. These mediators recruit macrophages and granulocytes to damage tissue, cause chronic inflammation and, finally, development of psoriasis [21-22]. IL-23 is mainly released by APCs to induce and maintain Th17 and Th22 cells' differentiation. Both cell lines are the primary cellular source of pro-inflammatory cytokines, which mediate epidermal hyperplasia, induction of keratinocytes and inflammation in Ps. IL-23 has a pivotal role in the activation of pathogenic Th17 cells resulting in tissue damage in different organs including joints [23].

The current model of Ps pathogenesis considers that it is a crosstalk between a complex network of dendritic cells in skin, T cells (predominantly Th17) and resident keratinocytes, which mediate inflammatory and immune responses resulting in development, progression and persistence of Ps [24]. It was found that injection of xenotransplant mouse model by neutralizing monoclonal antibody against IL-23 showed IL-23-dependent inhibition of psoriasis [25], Also, another study revealed that the blood levels of IL-23 were normal in transgenic mice *K23* but skin lesions precede the development of arthritis. So, high serum IL-23 concentrations, is not mandatory for the development of Ps, dactylitis and enteritis in *K23* mice and IL-23 might have a role in initiation and early stages of skin and joint involvement rather than in disease progression and late stages[26]. Thus, factors triggered by IL-23 in the skin (IL-17 and IL-22) can be pathogenic and cause joint pathology[27]. IL-22 was highly elevated in the sera of *K23* mice while its lack aggravated the arthritis like disease but not skin lesion[7]. In current study, when comparing Ps patients with controls regarding serum IL-23 level there was a statistically significant higher level in serum in Ps patients with much higher levels in those with PsA.

The aetiology of psoriasis arthritis is not yet clear. Whether, it is genetic, immunologic, or environmental but it seems all play a role. Up to 30% of Ps cases have PsA. The pathogenesis of PsA is complex[28]. First, high serum IL-23 concentrations can promote PsA via acting on an IL-23R positive cell population in patient's skin and in the entheses[29]. Secondly, Ps is a characterized by rapid epidermal cell turnover, which can cause hyperuricemia[30], and this was supported by our finding as regard increase the level of uric acid in PsA as compared to controls.

Interestingly, our study demonstrated that participants with either Ps or PsA have a statistically significant higher expression of IL-23R than controls. However, we found no statistically significant difference as regard IL-23R expression between Ps and PsA patients.

Also, the inflammation involves a large body area of psoriatic patients leading to increase in CRP. CRP causes elevation of blood pressure via decreasing nitric oxide (NO) in endothelial cells with subsequent vasoconstriction that impairs blood flow to the joint. Vasoconstriction results in hypoxia and impaired joint function leading to arthritis [31]. Moreover, cutaneous manifestations of Ps are because of impaired differentiation and proliferation of keratinocytes due to altered interaction between these cells and immune cells. Apart from skin, similar inflammatory reaction occurs at the joint causing PsA [32]. In addition, IL-23 induces the production, development and differentiation of functional and mature osteoclasts, signifying that it is a potent initiator of bone erosion and loss[33]. Furthermore, there might be shared pathogenic pathways between primary skin disease and PsA. This was augmented by the detection of identical T cell clones in skin and synovial tissues of PsA cases proposing that a shared antigen may be a driving immune response in both sites[34]. Finally, evidence exists regarding a partial overlap between Ps and PsA susceptibility genes, such as *HLA-Cw6* and other genes including *IL-13*, and *IL-23R* [35]. Interleukin-23 has been studied in a variety of systemic diseases including cancer, inflammatory and autoimmune diseases. Nonetheless, IL-23R expression in PsA remains unclear.To confirm the role of IL-23R expression in PsA, more research with large number of enrolled patients is required. It is crucial to investigate the involvement of IL-23 and its receptor in pathophysiology of Ps and PsA.

Finally, our findings declared the importance of serum IL-23 in diagnosis of Ps and prediction of PsA. Moreover, our data suggest a link between expression of IL-23R and the risk of Ps.

CONCLUSION

Interleukin-23 and its receptor have been proved to be significantly elevated and over-expressed in blood of psoriatic patients and may be used as diagnostic or therapeutic targets in psoriatic patients.

Conflict of interest: The authors declare no conflict of interest.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution: Authors contributed equally in the study.

REFERENCES

1. **Yamazaki F (2021):** Psoriasis: Comorbidities. Journal of Dermatology, 48(6): 48(6):732-740.
2. **Navardi S, Sahraian M, Doosti R *et al.* (2020):** Demographic and clinical characteristics of MS patients concomitant with psoriasis: Lower relapses, lower disability. Multiple Sclerosis and Related Disorders, 37: 1-1.
3. **Cannavò S, Bertino L, di Salvo E *et al.* (2019):** Possible roles of il-33 in the innate-Adaptive immune crosstalk of psoriasis pathogenesis. Mediators of Inflammation, 19:7158014.
4. **Roy A, Roy P, Grigorieva E (2018):** Mathematical insights on psoriasis regulation: Role of Th1 and Th2 cells. Mathematical Biosciences and Engineering, 15(3): 717-38.
5. **Shi Z, Wan Y, Hwang S (2020):** 318 Short-term exposure to Western diet (WD) predisposes mice to psoriasis-like skin and

joint inflammation. Journal of Investigative Dermatology, 140(7): 153-158.
6. **Mizumaki K, Horii M, Kano M *et al.* (2021):** Suppression of IL-23-mediated psoriasis-like inflammation by regulatory B cells. Scientific Reports, 11(1): 1-13
7. **Chen L, Deshpande M, Grisotto M *et al.* (2020):** Skin expression of IL-23 drives the development of psoriasis and psoriatic arthritis in mice. Sci Rep., 10:8259.
8. **Hua S, Yu X, Ma Y *et al.* (2019):** IL-23 and dendritic cells: What are the roles of their mutual attachment in immune response and immunotherapy? Cytokine, 120: 78-84.
9. **Ogawa E, Sato Y, Minagawa A *et al.* (2018):** Pathogenesis of psoriasis and development of treatment. Journal of Dermatology, 45(3): 264-272.
10. **Ma X, Shou P, Smith C *et al.* (2020):** Interleukin-23 engineering improves CAR T cell function in solid tumors. Nature Biotechnology, 38(4):448-459.
11. **Polese B, Zhang H, Thurairajah B *et al.* (2020):** Innate lymphocytes in psoriasis. Frontiers in Immunology, 11: 242.
12. **Nie W, Yu T, Sang Y *et al.* (2017):** Tumor-promoting effect of IL-23 in mammary cancer mediated by infiltration of M2 macrophages and neutrophils in tumor microenvironment. Biochemical and Biophysical Research Communications, 482: 1400-1406.
13. **Ghosh R, Mitra P, Goyal T *et al.* (2022):** T helper cells in depression: central role of Th17 cells. Critical Reviews in Clinical Laboratory Sciences, 59: 44-56.
14. **Huber S, Gagliani N, Esplugues E *et al.* (2011):** Th17 cells express interleukin-10 receptor and are controlled by Foxp3- and Foxp3+ regulatory CD4+ T cells in an interleukin-10-dependent manner. Immunity, 34: 554-565.
15. **Wu B, Zhang S, Guo Z *et al.* (2021):** The TGF-β superfamily cytokine Activin-A is induced during autoimmune neuroinflammation and drives pathogenic Th17 cell differentiation. Immunity, 54:308–323.
16. **Sun J, Zhang W, Chen W *et al.* (2019):** Effects of early enteral nutrition on Th17/Treg cells and IL-23/IL-17 in septic patients. World Journal of Gastroenterology, 25(22): 2799-2808.
17. **Banerjee S, Biehl A, Gadina M *et al.* (2017):** JAK–STAT signaling as a target for inflammatory and autoimmune diseases: Current and future prospects. Drugs, 77: 521-546.
18. **Koetzier S, Langelaar J, Blok K *et al.* (2020):** Brain-homing CD4+ T cells display glucocorticoid-resistant features in MS. Neurology(R) neuroimmunology & neuroinflammation, 7. https://doi.org/10.1212/NXI. 0000000000000894
19. **Huber A, Wang L, Han P *et al.* (2014):** Dysregulation of the IL-23/IL-17 axis and myeloid factors in secondary progressive MS. https://n.neurology.org/content/83/17/1500
20. **Carlin C, Feldman S, Krueger J *et al.* (2014):** A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. J Am Acad Dermatol., 50(6):859–866.
21. **Pastor-Fernández G, Mariblanca I, Navarro M (2020):** Decoding IL-23 signaling cascade for new therapeutic opportunities. Cells, 9(9): 1–33.
22. **Álvarez-Salamero C, Castillo-González R, Pastor-Fernández G *et al.* (2020):** IL-23 signaling regulation of pro-inflammatory T-cell migration uncovered by phosphoproteomics. PLoS Biol., 18(3): e3000646.
23. **Puig L (2017):** The role of IL 23 in the treatment of psoriasis. Expert Review of Clinical Immunology, 13(6):525-534.
24. **Chiricozzi A, Romanelli P, Volpe E *et al.* (2018):** Scanning the immunopathogenesis of psoriasis. International Journal of Molecular Sciences, 19(1): 179.
25. **Zheng Q, Liang S, Xu F *et al.* (2019):** C5a/C5aR1 pathway is critical for the pathogenesis of psoriasis. Frontiers in Immunology, 10: 1-12.
26. **Yamamoto M, Nakajima K, Takaishi M *et al.* (2015):** Psoriatic inflammation facilitates the onset of arthritis in a mouse model. Journal of Investigative Dermatology, 135(2): 445-453.
27. **Moermans C, Damas K,Guiot J *et al.* (2021):** Sputum IL-25, IL-33 and TSLP, IL-23 and IL-36 in airway obstructive diseases. Reduced levels of IL-36 in eosinophilic phenotype. Cytokine, 140: 1-8.
28. **Kivelevitch D, Mansouri B, Menter A (2014):** Long term efficacy and safety of etanercept in the treatment of psoriasis and psoriatic arthritis. Biologics: Targets and Therapy, 8: 169–182.
29. **Dudakov J, Cole D, Hanash A *et al.* (2012):** Intrathymic innate lymphoid cells: Long-lived mediators of immune regeneration. Blood, 122: 289.
30. **Khondker L, Khan S (2014):** Association of rheumatoid factor and uric acid with psoriatic arthritis: a review. Mymensingh Medical Journal, 23: 609-13.
31. **Sokolova M, Simon D, Nas K *et al.* (2020):** A set of serum markers detecting systemic inflammation in psoriatic skin, entheseal, and joint disease in the absence of C-reactive protein and its link to clinical disease manifestations. Arthritis Research and Therapy, 22: 1-6.
32. **von Stebut E, Boehncke E, Ghoreschi K *et al.* (2020):** IL-17A in psoriasis and beyond: cardiovascular and metabolic implications. Frontiers in Immunology, 10: 3096.
33. **Pang D, Cai L, Zhang J *et al.* (2020):** IL-23 induziert die Expression pro-osteogener Faktoren in Osteoklasten. Aktuelle Rheumatologie, 45(5): 467-474.
34. **Komech E, Barinova A, Shmidt E *et al.* (2021):** OP0027 as-related TCR beta clonotypes are present in different inflamed tissues of patients with spondyloarthropathies. Annals of the Rheumatic Diseases, 80(1): 1-2.
35. **Caputo V, Strafella C, Termine A *et al.* (2020):** Overview of the molecular determinants contributing to the expression of psoriasis and psoriatic arthritis phenotypes. Journal of Cellular and Molecular Medicine, 24(23): 1-10.