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Intercommunicating avenues – cytokine networks in psoriasis

Mihaela Surcel1, Adriana Narcisa Munteanu12, Carolina Constantin1,3, Monica Neagu1,2,3*

1 Immunology Department, Victor Babes National Institute of Pathology, Spl. Independentei 99-101, 050096, Bucharest, Romania
2 Doctoral School of Biology, Faculty of Biology, University of Bucharest, Spl. Independentei 91-95, 050095, Bucharest, Romania
3 Department of Pathology, Colentina University Hospital, Șos. Ștefan cel Mare 19-21, 020125, Bucharest, Romania

Abstract

Psoriasis is a systemic autoimmune disease in which skin's cells, keratinocytes, are hyper-activated and would actively secrete various immune molecules inducing the disease's immunopathogenesis. We are discussing herein the complex array of cytokine and chemokines that are intertwining and the mechanisms that are involved in Ps development along with our experience regarding the contribution of pro- and anti-inflammatory cytokines/chemokines in this autoimmune disease. We are presenting the cytokine network grouped by their action and regardless their origin, i.e. secreted by immune or non-immune cells. Moreover, we are discussing their molecular relationship that sustains cells' cross-talk in the development of psoriasis.

Key words:

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* **Corresponding author:**

Monica Neagu; neagu.monica@gmail.com

Introduction

Psoriasis (Ps) is a lifelong inflammatory T-cell mediated disease, with cutaneous and articular manifestations (Boehncke and Schön, 2015) having a significant negative impact on patients' quality of life. In the Global Report on Psoriasis (2016), WHO recognised Ps as a serious non-communicable disease affecting worldwide at least 100 million individuals. The report highlighted that many patients suffer as result of incorrect or delayed diagnosis, inadequate treatment options and social stigmatization (Global Report on Psoriasis, 2021). Ps is not only a skin condition that causes pain and disability, it is frequently associated with severe depression and anxiety that can lead even to suicidal tendencies (Lebowitz and Lebwohl, 2019).

The prevalence of this disease is increasing in both adults and children, and varies between 0.27% and 11.4%, depending on age, ethnicity, geographic area and environmental factors (Parisi et al., 2020). Thus, Ps occurs more frequently in adults than in children, it mainly affects the Caucasian population and is more common in high income countries. In children, the incidence of Ps increases with age, and the incidence rate is higher in girls than in boys. In females, the age of onset has a bimodal distribution, with two peaks at around 18-29 and 50-59 years, whereas in men a later onset has been reported, more commonly around 30-39 and 60-69 years (Parisi et al., 2020).

The exact causes of Ps are still not fully understood, is a complex skin condition where the altered immune system and the genetic predisposition inter-play inducing its aetiology (Ayala-Fontánez et al., 2016). Recent studies suggest that the Ps' onset and exacerbation are favoured by several extrinsic and intrinsic risk factors (Kamiya et al., 2019). Among the extrinsic risk factors several ones can be mentioned: exposure to sunlight and air pollution (Wolf et al., 2016), mechanical stress (Qiao et al., 2019), administration of certain drugs (Balak and Hajdarbegovic, 2017), vaccination (Wu et al., 2022), streptococcal infections (Zhou and Yao, 2022), smoking (Naldi, 2016), alcohol consumption (Kearney and Kirby, 2022). Various other deregulation named intrinsic risk factors can be associated with Ps, such metabolic syndrome (Hao et al., 2021), obesity (Wheatley et al., 2017), diabetes mellitus (Abramczyk et al., 2020), dyslipidaemia (Ikeda et al., 2022), hypertension (Song et al., 2022) and mental stress (Rousset and Halioua, 2018; Woźniak et al., 2021). Ps is also associated with several important medical conditions, including cardiovascular disease (Kölliker Frers et al., 2015), chronic kidney disease (Abuabara et al., 2010), other autoimmune diseases (Furue et al., 2018), and even cancer (Pouplard et al., 2013). Actually, multimorbidity is a common feature of the patients diagnosed with Ps. These comorbidities significantly affect the clinical management of this autoimmune disease and contribute to the increased mortality.

Clinically, Ps can be divided into pustular (generalized pustular Ps, impetigo herpetiformis, localized pustular Ps) and non-pustular (Ps vulgaris, guttate Ps, erythrodermic Ps, palmoplantar Ps, psoriatic arthritis, inverse Ps) variants. Ps vulgaris is the most common type of Ps and as in the other clinical forms, psoriatic lesions exhibit a series of common features, which include erythema, thickening and skin scaling (Sarac et al., 2016). Although the psoriatic lesions can affect any region of the body, knees, elbows, lumbosacral region, scalp, and genital area are most frequently affected. In severe cases, the entire skin can be affected (erythrodermic Ps). Ps exhibits a wide spectrum of skin manifestations and for this reason the specific clinical type is an important element in choosing the adequate treatment protocol.

The severity of Ps is established taking into account the affected skin surface (PASI score), the impact of the disease on the quality of life (DLQI score) (Strober et al., 2020), the way the disease is perceived and the resistance to treatment. The PASI score combines manifestations related to severity (erythema, induration and desquamation) and the percentage of the affected area, representing the gold standard to measure Ps' severity.

From the immune point of view Ps is a T-cell mediated skin disorder and, in its pathogenesis relies on the aberrant interplay between innate/adaptive immune cells and resident KC, interplay mediated by immune and non-immune molecules. The autoantigens involved in Ps' autoimmune reactions are still a research challenge, LL-37 (cathelicidin) produced by KC being the most studied autoantigen. Other pos-

sible autoantigens which are supposed to be involved in the pathogenesis of Ps are ADAMS-like-protein 5 produced by melanocytes, lipid antigens generated by PLA2G4D and keratin 17 derived from hair follicles (ten Bergen et al., 2020).

Two phases are commonly accepted to describe the Ps' pathomechanism: the initiation of psoriatic events and the maintenance of the inflammatory status. Within the inflammatory events, the immune cells are key players in both phases of the pathogenesis, namely the innate immune cells (DCs, Mø, NK cells) are involved in the early stages, while the adaptive immune cells (Th cell subsets) play a critical role in maintaining and perpetuation the chronic inflammation. Under the action of triggering factors (skin injury, infections, genetic and/or environmental factors), KC together with cells belonging to innate immunity (NK cells, Mø and pDCs) will start to hyper-secrete TNF-α, IL-1 β, IL-6, IFN-α, IFN-β, IFN-γ and further promote mDCs activation. Activated mDCs will determine the differentiation of naive T cells into Th17, Th1 and Th22 subsets through immune molecules like IL-12, IL-23, and TNF-α. Thereafter, IL-23, in association with IL-6 and TGF-β1, will determine the differentiation of naive T cells into Th17, cellular sub-population that will further secrete IL-17, IL-22 and TNF-α. These pro-inflammatory mediators will establish a self-sustained loop that will lead to hyper-activation of KC, cells producing large quantities of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines (CXCL1/2/3, CXCL8-11, CCL2, CCL20), antimicrobial peptides (LL-37, β-defensins), S100 proteins, maintaining and propagating the chronic inflammation (Georgescu et al., 2019; X. Zhou et al., 2022).

This complex process is also responsible for the histopathological features of psoriatic lesions namely acanthosis, hyperkeratosis, parakeratosis, elongation of rete ridges, and an abundant inflammatory cellular infiltrate consisting of neutrophils in *stratum corneum* and epidermis, mononuclear cells in the epidermis and leukocyte (T lymphocytes and DCs) in the dermis (Ayala-Fontánez et al., 2016). Consequently, in the skin an active crosstalk between immune cells and hyper-proliferative KC is unfolding through cytokines and their receptors, developing Ps' pathogenesis.

Overview of cytokine/chemokine network in Ps

As stated, hyper-activated KC would actively secrete various immune molecules that would induce the disease's immunopathogenesis (Sigurgrimsdottir et al., 2021). Alongside with the cellular component, cytokines hold a significant role in corroborating the immune responses in Ps, qualifying them as the most suitable targets to be used as therapeutic approaches (Baliwag et al., 2015). Therefore, modulating the cytokine signaling pathways is a strategy for diminishing psoriatic lesions (Mohd Noor et al., 2022).

The main cytokines involved in Ps development are IL-23, IL-17, IL-12, IL-22, ~~IL-23~~, IL-6, IL-10, IFN, TNF, TGF-β1, in which the key alterations are registered in IL-22/IL-23/IL-17 axis; this network of molecules induces an inflammatory process that sustains the proliferation of epidermal cells, neo-angiogenesis, and infiltration of DC in the skin (Surcel et al., 2017a; Georgescu et al., 2019). Besides the mentioned cytokines, stimulated KC will prolong the inflammatory setting by producing a large array of chemokines (e.g. CXCL1, CXCL2, CXCL3, CXCL5, CXCL8, CXCL9, CXCL10, CXCL20) (Hawkes et al., 2017). Releasing the immune molecules, IL-17, CXCL1, CXCL2 and CXCL8, becomes a squad that joins KC and Th17 cells in recruiting neutrophils to the psoriatic lesions. Thus, the recruited neutrophils will release large amounts of ROS, carrying out an increased respiratory burst and consequently intensifying the level of oxidative stress. The increase in the oxidative status will stimulate APC functions and would induce the formation of NETs (Shao et al., 2019). NETs are increased in the blood stream and correlate with the Ps' severity. Moreover, NETs create a very immunogenic milieu, being involved in the initial phase and maintenance of Ps, causing the epidermis to produce inflammatory cytokines following the cross-activation of receptors for TLR4 and IL-36 (Hu et al., 2016; Lee et al., 2017).

Inflammatory response related to the Ps pathophysiology starts when skin damage causes the KC to produce first TNF-α and IFN-γ; this primary cytokine - signal would further trigger IL-6 and CCL20 secretion by KC resulting in cell adhesion molecules activation and recruitment of immune cells from the blood stream to the injury site. KC secretory activity will sequentially stimulate pDCs to further se-

crete IFN-α and IFN-γ in order to activate mDCs and skin's Langerhans cells. These APC cells, resident of the skin, will be directed to the lymph nodes to stimulate differentiation of naïve Th cells (Th0) in Th1, Th17 and Th22 subpopulations. These differentiated T lymphocytes will return to the skin tissue and will produce yet again pro-inflammatory specific cytokines, namely IL-2, TNF-α, IFN-γ (Th1), IL-6, IL-17, IL-21 and IL-22 (Th17) and IL-22 (Th22). The propagation of the inflammatory response is sustained by the influx of innate immune cells (neutrophils, Mø, NK, mast cells) to the injury site, that in turn would secrete more cytokines (IL-1β, IL-6, IL-8, IL-17, IL-22, TNF-α, IFN-γ), thus completing the picture of immune molecules that intervene side by side with the immune cells in the pathogenesis of Ps (Boehncke and Brembilla, 2018; de Alcantara et al., 2021; Rendon and Schäkel, 2019).

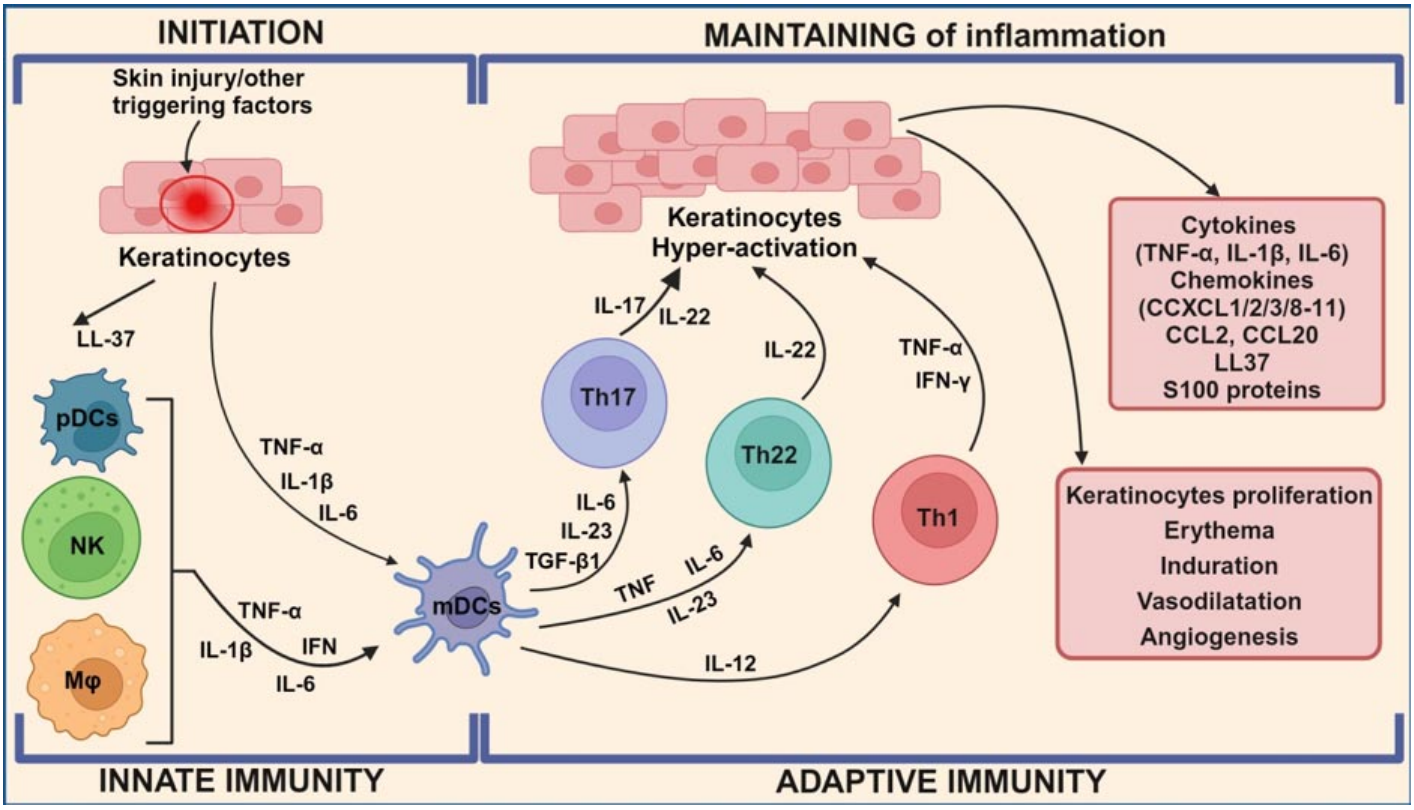
However, the cellular and humoral basis of Ps pathogenesis relies also on a strong genetic background that includes genetic variants of cytokines. Thus, over 400 genes containing SNV are associated with Ps, most of them being related to the immune response network. In addition, by using genome-wide studies, over 40 susceptibility loci have been found to be associated with Ps (Singh et al., 2019). Moreover, these genes are linked to T lymphocytes signaling, APC functionality and skin barrier proper integrity (Pușcaș et al., 2023). Additionally, ten chromosomal regions named *psoriasis-associated susceptibility locus* (*PSORS*) were found significantly associated with Ps. Specifically, *PSORS1* located in the MHC region on chromosome 6, is supposed to be responsible for Ps heredity in a high percentage of 35–50% (Babaie et al., 2022; Gupta et al., 2014), while *HLA-Cw6* allele is allegedly associated with type I, namely early-onset of Ps (L. Chen and Tsai, 2018).

A graphical outline of Ps' pathomechanism where non-immune and immune cells cross-talk through cytokines/chemokines network is depicted in ***Figure 1.***

Pro-inflammatory cytokines in Ps

IL-12(p70) and IL-6

Important mediators of immune response, IL-12 and IL-6, were proven highly involved in the Ps pathogenesis. Cellular immune mechanisms are triggered within this autoimmune disease, hence naive T-CD4$^+$ cells are activated when antigen-MHC complex is established and, depending on the tissue microenvironment (e.g. cytokines and chemokines) they can differentiate into a variety of effector subsets (Martinez-Sanchez et al., 2018), including Th1 and Th17



cells. These types of lymphocyte subsets are key players in Ps pathogenesis. Within the skin's microenvironment, IL-12 and IL-6 regulate Th1/Th2 differentiation. Therefore, IL-12 induces the differentiation into Th1 cells, while IL-6 promotes the IL-4-dependent induction of Th2 differentiation and inhibites Th1 polarization (Zeng et al., 2022). IL-6 is similarly involved in the differentiation of Th17 cells in the presence of IL-23 (Cataldi et al., 2019).

IL-12 was discovered by Trinchieri's group (more than 30 years ago) and independently by Gately's group and was named as "natural killer–stimulating factor" and as "cytotoxic lymphocyte maturation factor", respectively by the two groups (Kobayashi and Fitz, 1989; Stern et al., 1990). Il-12 is a heterodimeric molecule, produced by DC, Mø, neutrophils and B lymphocytes as a response to antigenic stimulation. It is an important immune molecule because IL-12 has an extended family comprising IL-23, IL-27 and IL-35 (Vignali and Kuchroo, 2012). In Ps, IL-12 and IL-23 are secreted by mDCs, these dendritic cells being the main activated cells by TNF-α, IFN-γ, IL-1β and IL-6, cytokines secreted by both KC and immune cells (e.g. NK, Mø, DC. Both IL-12 and IL-23) that are responsible for the differentiation of naive T cells into Th1, Th17 and Th22 cells. Upon differentiation, these effector T cell subsets will actively secrete TNF-α, IFN-γ, IL-17 and IL-22, in a loop that activates KC to produce an array of immune molecules, mainly pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines (CXCL9-11), antimicrobial peptides (LL-37, β-defensins) and S100 protein. Moreover, activated KC will attract and further activate neutrophils and Mø, cells that will promote and maintain the inflammatory processes in Ps (Georgescu et al., 2019).

Figure 1
Ps' pathomechanism.
Under the action of triggering factors (skin injury, infections, genetic and/or environmental factors), KC together with NK cells, Mø and pDCs activate mDCs mainly through TNF-α and IFN-γ. Activated mDCs cells promote the differentiation of naive T cells into Th17, Th1 and Th22 through IL-12, IL-23, and TNF-α. These effectors will secrete TNF-α, IFN-γ, IL-17, and IL-22 leading to hyper-activation of KC which will produce mainly pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines (CXCL1/2/3/5/8), antimicrobial peptides (LL-37, β-defensins), S100 proteins, thus maintaining the inflammatory status.
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At molecular level IL-12 and IL-23 are heterodimers having in common the p40 subunit; this molecule was reported as overexpressed in Ps lesions. By imposing inhibition on p40 subunit, the downstream effects of both IL-12 and IL-23 are blocked (Jeon et al., 2017). IL-12 is a therapy target in Ps, anti-IL-12 therapy is efficient leading to a decreased level of IFN-γ (Jeon et al., 2017). In Ps patients PASI score evaluates the severity of the disease and it was reported that IL-12 has increased serum levels (Brito-Luna et al., 2016) positively correlated with PASI (Takahashi et al., 2010). In IMQ-induced Ps mice, increased IL-12 levels were reported in both spleen and skin (Liu et al., 2018).

Another IL involved in Th2 and Th17 differentiation is IL-6; this cytokine is a pleiotropic proinflammatory molecule highly involved in a myriad of inflammatory-mediated diseases, including Ps. Specifically in Ps, IL-6 is secreted mainly by KC, DC, Mø and Th17 cells. IL-6 was discovered as a myokine that is appearing in the blood stream after exercise (Bruunsgaard et al., 1997). Then it was shown elevated in the blood circulation in many diseases, from skin melanoma (Neagu et al., 2013) to metabolic disorders (Sadagurski et al., 2010; Neagu and Dobre, in press) and from neurodegenerative diseases (Swardfager et al., 2010) to autoimmune diseases. The finding that in Ps patients this cytokine is elevated drove the research to the development of anti-IL-6 therapies in Ps. Nevertheless, anti-IL-6 treatment did not have the expected effect in Ps. Therefore, the anti-IL-6 therapies that were efficiently applicable for rheumatoid arthritis, were proven ineffective for Ps or even inducing a new-onset of Ps-like disease (Blauvelt, 2017). In an IL-6-deficient genetic mouse model, Fritz et al, demonstrated that the therapeutic IL-6 blockade in humans induces a compensatory increased production of other pro-inflammatory cytokines at skin level (Fritz et al., 2017).

As elevated serum levels of IL-6 have been reported in both humans diagnosed with Ps and mice model of Ps (Liu et al., 2018) it was recommended that IL-6 should be viewed as a marker of disease and not as a therapy target. Thus, IL-6 can be a treatment response biomarker to various biologics in Ps therapy (Bai et al., 2017; Muramatsu et al., 2017). Our results also revealed a high serum level in IMQ - Ps experimental model, namely IL-6 serum level was found 8 times higher as compared to controls. Moreover, the strong negative correlation that we have found between IL-6 and IL-12 (p70) in Ps animal group brings additional proof that there are cellular regulatory processes between IL-6 and IL-12 secretion (Surcel et al., in press).

TNF-α and IFN-γ

In Ps, IL-12 will promote the differentiation of naive T cells into Th1 cells, activation that will enhance the secretion of pro-inflammatory cytokines including IL-2, TNF-α and IFN-γ. The secreted array of pro-inflammatory cytokines, along with IL-17 and IL-22, will hyper-activate KC that will produce yet again pro-inflammatory cytokines/chemokines. This self-enhanced autoimmune process will contribute to the perpetuation of the inflammatory status (Surcel et al., 2019).

TNF-α is a pleiotropic cytokine that is produced by many cell types as a response to infection or tissue injury, exerting various functions on several cell types (Conrad et al., 2018). Historically, TNF was discovered almost 60 years ago by two independent groups, being reported as a cytotoxic factor produced by lymphocytes and initially being named lymphotoxin (LT) (Kolb and Granger, 1968; Ruddle and Waksman, 1968). Its known name, *Tumor Necrosis Factor*, arose after another 10 years (Carswell et al., 1975) and after another 10 years, in the dawn of genetics, when cloning the genes for LT and TNF (Pennica et al., 1984), it was established that LT and TNF were the same molecule.

TNF-α is secreted by activated DC, KC, NK, Th17 and Th1 cells and is a key cytokine mediating the un-controlled inflammatory processes associated with Ps. When anti-TNF-α's therapies were developed they induced good clinical outcome in Ps patients. When TNF-α and IL-17 inhibitors were applied in a dual regimen they more effective than the individual ones (Fischer et al., 2015).

IFN-γ involvement in Ps was acknowledged for a long time, but the discovery of IL-23 and the identification of Th17 cells have brought a new player on the cytokine scene. Therefore, recent experimental and clinical studies have revealed the importance of the IL-23/Th17 axis, as well as the associated molecules, TNF-α, IL-23, IL-17 and IL-22, that can become important therapeutic targets in Ps (Bugaut and Aractingi, 2021). As IL-23/IL-17 cytokine axis is viewed as a major driver of Ps, recent studies recapitulate a loop route relation between IL-23 and IL-17 actions. Thus, IL-23 expressed by immune cells (mDC) seems mandatory for the expansion of IL-17-producing Th cells (Griffiths et al., 2021). Additionally, a recent report using a genetic mouse model of Ps, reinforced that KC-derived IL-23 sustains the IL-17 secretion leading to a chronic skin inflammation. When activated by these cytokines, mainly IL-17, KC will produce an array of inflammation contributors such as cytokines, chemokines, and even antimicrobial peptides (Ni and Lai, 2020). Further studies have inquired also the epigenetic fingerprint of cytokine secretion and found that epigenetic regulation by H3K9 dimethylation has controlled IL-23 expression in KC, which is again recognized as a trigger for Ps onset (Kruszniewska-Rajs et al., 2022; H. Li et al., 2018; Zhou and Yao, 2022).

TNF-α and IFN-γ serum levels were found both elevated in the serum of Ps patients (Cataldi et al., 2019) and these levels were correlated with PASI score (Takahashi et al., 2010), hence reinforcing the increased Th1/Th17 cytokine profile in Ps patients (Bautista-Herrera et al., 2018). In Ps experimental models it was reported that the increased serum of TNF-α correlates with tissue expression in secondary lymphoid organs tissue (e.g. spleen) and in skin (Liu et al., 2018). Our data is in accordance with the earlier reports and reveal highly increased serum levels of TNF-α in Ps mice model. Moreover, we have established for the first time a strong negative correlation between IFN-γ and IL-12 (p70) in Ps group. The mechanistic behind this correlation can be explained by the predominance of other Th1 specific cytokines, e.g. TNF-α, in the psori-

atic inflammatory events (Surcel et al., in press).

IL-1α and IL-1β

IL-1 discovery has probably the longest cytokine history because its research started in the late 40s when the pathogenesis of fever was studied (Dinarello, 2015). In 1985, two distinct, DNAs encoding proteins both having IL-1 activity were reported and thus the two individual members of the IL-1 family were defined, IL-1α and IL-1β (March et al., 1985)

Actually, the pro-inflammatory cytokine IL-1 was the first cytokine detected in skin. The two members of the large IL-1 family of proteins, IL-1α and IL-1β, have 11 ligands that address to 9 receptors. IL-1 family has important functions in both innate and adaptive immune response, but this family is also associated with exacerbated inflammation (Matarazzo et al., 2022). Through this uncontrolled and exacerbated inflammation, IL-1 family is involved in Ps pathogenesis. IL-1 family is involved in skin barrier functionality; therefore if skin's functional integrity is deregulated it can induce various pathological conditions. It is a seminal cytokine that can induce inflammatory-related diseases linking innate and adaptive immunity responses (Matarazzo et al., 2022). It is interesting how IL-1α and IL-1β balance each other in skin's pathology. Tamilselvi et al identified IL-1α reduced level in both skin biopsy and plasma samples from patients diagnosed with Ps. Upon treatment with methotrexate, IL-1α levels increased significantly. IL-1β was reported as having increased levels and following treatment with methotrexate the level decreases (Tamilselvi et al., 2013). In our IMQ experimental model we have obtained similar results, namely the same variation of IL-1α and IL-1β. Thus, we have obtained significant decreased mean values for IL-1α in Ps-mice as compared to controls, values that were strongly positively correlated to TNF-α values and negatively correlated to IL-1β (Surcel et al., 2023). We have found an interesting dynamic of serum IL-1β that was found highly increased in Ps mice, but after the natural healing of the psoriatic lesions, the IL-1β values remained increased proving that this cytokine has a higher remanence in circulation. The remanence of IL-1β after the skin's lesions are healed is correlated with cells that are secreting this cytokine.

We have obtained a strong positive correlation between IL-1β and IL-12 (p70) in Ps animal model. This finding suggests a strong synergic action of these pro-inflammatory cytokines even after the healing process has subsided and probably these cytokines are still active, as being involved in the normal regenerative process of the skin. Moreover, the correlation can be as well explained by Mø plasticity in inflammation and the polarization towards the M1 population that induces both high IL-1β and IL-12 secretion (Dissanayake et al., 2021).

As shown above for IL-12 and IFN-γ, in our IMQ-Ps induced experimental model, we have obtained also a strong negative correlation between IL-1β and IFN-γ in induced Ps. This correlation has some complex recently reported subjects. mTOR bestows T cells and other immune cells with the capability to sense and integrate diverse environmental signals together with nutrients and growth factors (Chi, 2012; Jones and Pearce, 2017). mTORC1 and mTORC2 are involved in γδT cell differentiation mediating the activity of γδT cells in tumors and in autoimmune diseases (Yang et al., 2020). Recent studies have shown that IL-1β promotes mTORC2 activation and chemotactic activity of IFN-γ+ γδ T cells (Liu et al., 2022). Therefore, in the light of these findings the negative correlation that we have reported can be explained by the high inflammatory status induced by Ps that counterbalances these two cytokines, balance that is regulated by mTORC2 activation. Moreover, we do not rule out that other cytokines from the pro-inflammatory arsenal counterbalances IFN-γ, detectable only in Ps group (Surcel et al., 2023).

IL-9, IL-15 and IL-17

IL-9 belongs to the IL-2 cytokine family and has pleiotropic immune functions. It was discovered more than 30 years ago in Th cell lines that were proliferating without antigen specific stimulation (Uyttenhove et al., 1988). Although initially IL-9 secretion was linked with Th2 phenotype, consequently it was shown that IL-9 is produced by Th-9 cells as a response to IL-4 and

TGF-β stimulation (Goswami and Kaplan, 2011). The significance of IL-9 in Ps was shown when discovering Th17-mediated inflammation and angiogenesis (Singh et al., 2019) and its direct involvement in the formation of psoriatic lesions (Deng et al., 2017). Midde et al demonstrated in Ps development that IL-9 is the link between systemic inflammation and angiogenesis. The report suggested the existence of a pro-inflammatory milieu that abounds in cytokines (IL-9, IL-17) and VEGF, and that this trio of molecules associates an increased severity of Ps (Midde et al., 2021). In an IMQ-Ps mouse model we have shown increased levels of IL-9 compared to controls and a strong negative correlation between IL-9 and IL-15 in Ps group. IL-15 signals through a heterotrimeric receptor that has a common gamma chain (γc) shared with multiple cytokines (IL-2, IL-4, IL-7, IL-21), among which IL-9 (Waldmann, 2013). As they are structurally similar, we do not rule out that their functions compensate each other in the Ps pathology. For naturally healed mice serum IL-9 concentration decreased to the control values. Another correlation that we have reported in IMQ - induced Ps experimental model is that IL-9 serum levels are strongly positively correlated with IL-6 level and negatively correlated with IL-12 levels (Surcel et al., 2023). These complex immune cross-talks in the cytokine network still have to be deciphered and IL-9 remains an understudied cytokine although it is involved in many immune/biological functions.

IL-15 is a pro-inflammatory pleiotropic cytokine secreted mainly by Mø, monocytes and DCs; IL-15 is highly involved in the growth, development and survival of NK cells, it is a potent chemoattractant for leukocytes and a strong inhibitor of KC apoptosis (Isvoranu et al., 2021; Rückert et al., 2000). Discovered in 1994 due to its functionality that is similar to IL-2, IL-15 expression is up-regulated under inflammatory conditions and induces the production of other pro-inflammatory cytokines (e.g. TNF-α, IFN-γ, and IL-17) (Isvoranu et al., 2021). In Ps, IL-15 and its specific receptor are overexpressed being involved in the pathogenesis of this autoimmune disease. Twenty years ago, it was reported in a xenograft mouse model, the almost complete resolution of Ps after blockade of IL-15 biological activity, these data being one of the first one that supports the role of IL-15 in Ps pathogenesis (Villadsen et al., 2003). Our data obtained on IMQ-induced Ps in animal model show significantly elevated IL-15 serum levels and a significant decrease after natural healing of the psoriatic lesions. We also noticed a strong positive correlation between IL-15 and IFN-γ in IMQ -induced Ps mice (Surcel et al, 2023). Recently it was shown in an autoimmune skin disease (*Persistent Erythema Multiforme*) that in lesional skin, IFN-γ and IL-15 are highly up-regulated and subsequently suppressed following tofacitinib treatment (Murphy et al., 2021). As noted, the correlation is due to the fact that IL-15 induces the production of other pro-inflammatory cytokines (e.g. TNF-α, IFN-γ, and IL-17).

From the group of cytokines that we are elaborating on, IL-17 is highly involved in autoimmune diseases and thus in Ps pathogenesis. IL-17 family of cytokines was originally discovered by Rouvier et al. in 1993 (Rouvier et al., 1993) and subsequent studies have shown that the most important member of IL-17 family is IL-17A. IL-17A is also a pro-inflammatory cytokine produced by Th17 cells (but not exclusively) through IL-23 signaling. IL-17A is involved in the induction and mediation of pro-inflammatory immune responses. In psoriatic lesions IL-17A expression are increased and would induce directly on KCs the expression of other pro-inflammatory molecules, perpetuating the inflammatory status in Ps (de Alcantara et al., 2021). IL-17A has become an important therapeutic target in Ps. In the later years, several anti-IL-17 agents were implemented in clinic for the treatment of moderate-to-severe plaque Ps (ixekizumab, secukinumab, and brodalumab) (Jeon et al., 2017). In psoriatic lesions and in peripheral blood increased levels of Th17 cells and IL-17A were reported (de Oliveira et al., 2015) and these parameters were found positively correlated with PASI score, hence with the gravity of the disease (Midde et al., 2021). Earlier, Bai et al, reported that there are no differences between Ps patients and controls for IL-17, but in men diagnosed with Ps there is an increased serum levels of IL-17 (Bai et al., 2017). Our study on IMQ-Ps animal model, showed IL-17 higher

serum level in Ps mice and normalization of values after naturally healed mice. It is interesting that, similar to Bai et al report, IL-17 serum levels were statistically significant different in Ps male mice compared to control males, differences that were not observed in females (Surcel et al., 2023). As the finding seems surprising, the explanation of the gender-related cytokines levels was previously reported by us in other skin related pathologies (Surcel et al., 2017b) and earlier by other groups in autoimmune diseases (Fairweather et al., 2008). Serum levels of IL-17 in Ps induced animals were strongly positive correlated to IL-15, this correlation is expected as IL-15 triggers IL-17 production as previously reported data in other autoimmune diseases (Ziolkowska et al., 2000).

Anti-inflammatory cytokines in Ps IL-5, IL-10 and IL-13

Anti-inflammatory cytokines (Th2-specific cytokines) have been less studied in Ps because the research focused mainly on the Th1/Th17 profile. In a study regarding psoriatic arthritis, no significant differences were observed for Th2 cytokines, while Th1 and Th17 cytokine levels were significantly increased (Bautista-Herrera et al., 2018). Although the level of Th2-specific cytokines does not seem to differ compared to normal subjects, Priyadarssini et al reported an imbalance in T-cell immunophenotype, characterized by an increase in Th1/Th17 cells and a relative decrease in Th2/T-reg cells (Priyadarssini et al., 2016). In our IMQ-Ps experimental model we have found IL-5 and IL-10 elevated serum levels in Ps group, while IL-13 showed significantly decreased values as compared to controls. For natural remission of the induced Ps we also obtained decreased mean values. We have found a strong positive correlation between IL-13 and IL-10, and a negative one between IL-13 and IL-1β in IMQ mice. These correlations prove once more the balance between Th1 and Th2 cytokine's profiles (Surcel et al., 2023). We do not rule out that the experimental IMQ-animal model does not perfectly mirror an auto-immune human disease; therefore, it is highly possible that in Ps' patients other additional mechanisms could be relevant, mechanisms that are not generated also in the mouse animal model. Earlier studies have shown that a therapy with IL-4 and IL-10 may ameliorate psoriatic skin lesions (Roberti et al., 2014), due to their action of inhibiting IL-1β, IL-6 and Th17 producing cells (Guenova et al., 2015; Onderdijk et al., 2015).

Inflammatory chemokines' in Ps model

Chemokines were first discovered in the late 1980s due to their *in vitro* action, namely molecules that have leukocyte chemoattractant activity and are secreted by activated human mononuclear leukocytes (K. Chen et al., 2018). Chemokines are important molecules in various diseases from skin tumors (Neagu et al., 2015) to autoimmunity. In Ps pathogenesis chemokines are responsible for the recruitment of leukocytes within the site of inflammation. They are mainly involved in the maintenance phase of inflammation in Ps, and can become biological markers of disease severity (Zdanowska et al., 2021).

MCP-1/CCL2, MIP-1α/CCL3 and MIP-1β/CCL4

There is a large array of molecules with chemoattractant activity, and since their discovery more than 50 chemokines and 20 subsequent specific chemokine receptors were found (Ruffini et al., 2007). Chemokines are classified in four subfamilies based on the number and location of the N-terminus cysteine residues therefore are named CXC, CC, CX_3C, and C (Rollins, 1997).

Out of the numerous families of chemokines we will elaborate on the most important ones in Ps. MCP-1/CCL2 is an inflammatory chemokine and in Ps is produced mainly by KCs. MCP-1/CCL2 binds to its specific receptor expressed by monocytes, inducing the migration of monocytes from the blood stream to the inflammation sites. Circulating monocytes become Mø that will act as antigen-presenting cells (APC). In the process of developing the immune response, APC will secrete TNF-α, a factor that actively contributes to the formation of Ps lesions (Behfar et al., 2018). Almost 10 years ago it was reported that Ps patients have elevated plasma levels of MCP-1/CCL2 and after anti-TNF-α therapy a moderate decrease is noted. Based on these observation MCP-1/CCL2 can be an in-

flammatory marker of disease's severity and moreover a marker of anti-TNF-α treatment efficacy (Lembo et al., 2014). Our recent data on IMQ – induced Ps in animal model show an elevated level of MCP-1/CCL2 in Ps group as compared to healthy mice (Surcel et al., 2023). Moreover, we have found strong positive correlation of MCP-1/CCL2 with IL-12 (p70), and a strong negative correlation with IFN-γ in Ps group. These findings are explained by the MCP-1 and IL-12 synergic action that aim to enhance the recruitment and activation of innate immune cells (B. Li et al., 2010). This chemokine is not specific to a disease, is specific only to the inflammatory status, therefore it was found significantly increased also in other models of skin cancers (Surcel et al., 2017b).

Over 30 years ago, a protein doublet that sustained the inflammatory activity of endotoxin-stimulated murine Mø (Napolitano et al., 1991) was discovered and named macrophage inflammatory protein-1 (MIP-1). Actually, the protein doublet consisted of two highly related proteins, MIP-1α and MIP-1β, having 68% identical amino acids sequences (Zlotnik and Yoshie, 2000). MIP-1α/CCL3 and MIP-1β/CCL4 are chemo-attractants for eosinophils, monocytes, B cells, and immature DCs and are potent activators for Mø. They have interesting completing functions, hence while MIP-1α/CCL3 selectively attracts T-CD8$^+$ lymphocytes, MIP-1β/CCL4 attracts T-CD4$^+$ lymphocytes (Zdanowska et al., 2021). In Ps patients, Dai et al reported significantly higher serum levels of MCP-1/CCL2, MIP-1α/CCL3 and MIP-1β/CCL4, all these chemokines were found positively correlated with the PASI score, and after acitretin therapy, these chemokines had significantly decreased values (Dai et al., 2014). Our data show that in IMQ-mice experimental model high serum levels were obtained for induced Ps and moreover MIP-1α/CCL3 and MIP-1β/CCL4 positively correlated with circulating T-CD3$^+$ (Surcel et al., 2023).

KC/CXCL1, IP-10/CXCL10 and MIG/CXCL9

The CXCL extended family is another chemokine group highly involved in Ps. CXCL1, discovered also in the 1980s had initially numerous denominations, GRO1 oncogene, GROα, neutrophil-activating protein 3 (NAP-3), melanoma growth stimulating activity, alpha (MGSA-α) and so on. When it was first cloned from a cDNA library induced by platelet-derived growth factor (PDGF) stimulation of 3T3 murine embryonic fibroblasts it gained the "KC" name for its location in the nitrocellulose colony hybridization assay (Cochran et al., 1983). CXCL1 is involved in wound healing and inflammation; it is a potent attractant for neutrophils, which are involved in the formation of intra-epidermal Munro's micro abscesses. In Ps skin lesions, CXCL1 is abundantly produced by hyper-proliferative KCs after IL-17, IL-22 and TNF-α stimulation (Albanesi et al., 2018). CXCL1 is a highly inflammatory chemokine and it was found in other inflammatory mediated diseases that involve skin pathology having high circulatory levels in melanoma animal models (Surcel et al., 2017b).

Th1 cells are recruited at the inflammatory sites after the pair's chemokine-specific chemokine receptor are established, namely CXCL9, CXCL10 and CXCL11 binding to CXCR3 which are secreted mainly by KCs after IFN-γ stimulation (Kanayama et al., 2021). In early stages of Ps, Ferrari et al reported increased serum concentration of IP-10/CXCL10 that proves a Th1 profile, and when Ps enters its chronic stage this chemokine decreases (Ferrari et al., 2015). Obesity and its relation with Ps are intensively studied in recent years (Constantin et al., 2023) and the involvement of chemokine in the overall inflammatory status. Therefore, when studying chemokines associated to Ps in context of obesity, high MIG/CXCL9 plasma levels were reported in earlier studies. In 2015 it was for the first time demonstrated that chemokines increase when the autoimmunity is installed and the metabolic disorder contributes less to the chemokine pool (Duarte et al., 2015). Our results in IMQ-mice have shown increased serum levels for all these mentioned chemokines and a decreasing trend after natural healing. It is interesting that KC/CXCL1 serum level in naturally healed mice after induced Ps remained elevated, opposite to IP-10/CXCL10 serum kevel that decreased to the control's values (Surcel et al., 2023). Similar to human studies, in our Ps–induced mice the KC/CXCL1 circulatory values positively correlated with TNF-α values. This finding was previously reported in endothelial cells subjected to inflammation where it was shown that TNF-α

induces directly CXCL1 over-expression (Lo et al., 2014). In our experimental model MIG/CXCL9 values were found positively correlated to IFN-γ. This correlation is explained by CXCL9 that polarizes and activates T cells to the Th1 immune arm; these cells will produce IFN-γ, TNF-*a*, IL-2 (Mosser and Edwards, 2008). Actually, there is an IFN-γ-CXCL9 loop where interferons activate the CXCL9 release and the chemokine induces interferons production (Tokunaga et al., 2018).

Conclusion

Pro-inflammatory cytokines and chemokines studies are a never ending story in various pathologies, including autoimmune diseases, and therefore Ps. The cytokine network has as central players, TNF-α, IL-6, and IL-1β, and as central chemokine CXCL1. There is a complex collection of cytokine and chemokines that are intertwining and are initiating mechanisms that trigger and sustain Ps. Regardless of their origin, i.e. secreted by immune or non-immune cells, cytokine - chemokine network establish molecular relationship that sustains cells' cross-talk and that contribute to the development of the autoimmune disease.

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List of Abbreviation

ADAMS-like-protein 5 – a disintegrin and metalloprotease domain containing thrombospondin type1 motif like 5
APC – antigen-presenting cells
CD – Cluster of Differentiation
CXCL9-11 – chemokine (C-X-C motif) ligand 9-11
DC – dendritic cells
DLQI – dermatology life quality index
H3K9 – histone H3 lysine 9
IFN – interferon
IL- interleukin
IMQ – imiquimod
KC – keratinocyte
LL-37 – leucine-leucine-37; cathelicidin
LT – lymphotoxin
Mø – macrophage
MCP-1 – monocyte chemoattractant protein-1
mDCs – myeloid dendritic cells
MIF – macrophage migration inhibitory factor
MIP – macrophage inflammatory protein
mTOR – mammalian/mechanistic target of rapamycin
mTORC1 – mammalian target of rapamycin complex 1
NK – natural killer cells
NET – neutrophil extracellular traps
PASI – psoriasis area severity index
pDCs – plasmacytoid dendritic cells
PLA2G4D – phospholipase A2 group IVD
Ps – psoriasis
PSORS – psoriasis-associated susceptibility locus
ROS – reactive oxygen species
S100 – protein soluble in 100% ammonium sulfate
SNV – single nucleotide variation
Th – helper T lymphocyte
TLR – Toll-like receptor
TGF – transforming growth factor
TNF – tumor necrosis factor
WHO – World Health Organization

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Competing interests/conflict of interests

The authors declare no conflict of interests.

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