

Received: December 19, 2016
 Accepted: January 20, 2017
 Published: January 25, 2017

Better Understanding the Immunopathogenesis of Psoriasis

Ana Paula Galli Sanchez*

Dermatologist and Master of Science from the Medical College of the University of São Paulo; São Paulo-SP, Brazil

*Corresponding author: Ana Paula Galli Sanchez, Dermatologist and Master of Science from the Medical College of the University of São Paulo; Medical contributor to severe psoriasis clinic of the Hospital Ipiranga, São Paulo-SP, Brazil, E-mail: apc-med@hotmail.com

1 Abstract

The immunopathogenesis of psoriasis involves complex interactions between the innate and the adaptive immune system, with emphasis on participation of keratinocytes, neutrophils, dermal dendritic cells and T lymphocytes. The knowledge of the immunopathogenesis of the disease is essential for understanding the mechanism of action of several systemic medications used in the treatment of the disease, especially the biologics. In this article the main and current knowledge of the immunopathogenesis of psoriasis is summarised.

2 Keywords:

Immunology; Psoriasis; Cytokines; Interleukin-23; Interleukin-17; Tumoral Alpha Necrosis Factor;

3 Introduction

Psoriasis is a common, chronic immune-mediated inflammatory skin disorder [1-5]. In genetically predisposed individuals, environmental factors cause an exaggerated activation of the Innate Immune System (IIS) and the Adaptive Immune System (AIS), leading to excessive proliferation of keratinocytes and the appearance of skin lesions [1-5].

Initially there is a hyperactivation of IIS cells, especially keratinocytes, dermal Dendritic Cells (DC) and macrophages [1-5].

The IIS cells are activated via receptors that recognize molecular patterns that are repeated in several pathogens (Pathogen Recognition Receptors - PRR); through molecules produced in cellular stress situations (such as the heat shock proteins - HSP and the antimicrobial peptides - AMP) or via other cytokines produced by activated cells [2, 3]. In psoriasis there is enhanced expression of "Toll Like Receptors" (TLR) on the keratinocytes and on the DC (TLR is a type of PRR) [2, 3]. It occurs also excessive production

of HSP and AMP by keratinocytes [1-3]. Moreover, there is increased expression of several genes that participate in innate immune (and adaptive) responses [2, 4-6]. Activated keratinocytes, DC and macrophages produce various proinflammatory cytokines such as interleukin (IL) 1, IL-6, tumoral alpha necrosis factor (TNF- α) and interferon (INF) [1-4].

In the early development of lesions, it appears to be essential the activation of the plasmacytoid dendritic cells (pDC), producing INF- α [2-4]. INF- α and other proinflammatory cytokines (produced mainly by activated macrophages and keratinocytes) promote an excessive activation of the myeloid dermal dendritic cells (mDC), whose number is much increased in psoriatic plaques (Figure 1) [1-5].

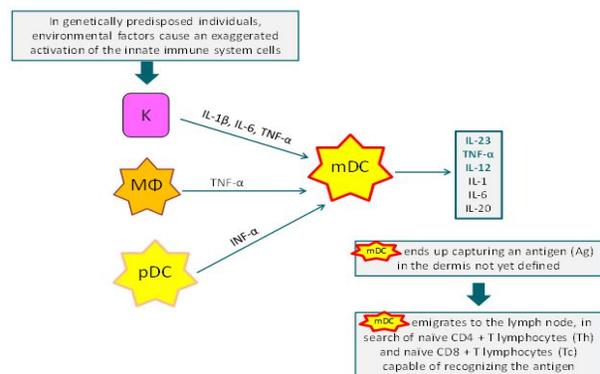


Figure 1: Innate immune cells involved in the early immune response of psoriasis: keratinocyte (K), macrophages (M Φ), plasmacytoid dendritic cell (pDC), myeloid dendritic cell (mDC). IL: interleukin; TNF- α : tumoral necrosis factor alpha; INF- α : interferon alpha; Th: T helper lymphocyte; Ag: antigen.

The mDC, in turn, are sources of various cytokines (IL-23, TNF- α , IL-12, IL-6, IL-1 and IL-20) and end up capturing a protein antigen (Ag) in the dermis not yet defined [1-5]. Some authors believe that this Ag can be a protein from the skin microbiota [7]. Others suggest that it is the LL-37 (AMP that may form a complex with self-RNA or self-DNA, leading to the activation of DC

through TLR) [2-4]. A recent study highlights the participation of a melanocyte protein as the possible Ag of the disease [8].

Anyway, after capturing and processing the Ag, the mDC emigrate to the lymph node, in search of naïve CD4 + T lymphocytes (Th) and naïve CD8 + T lymphocytes (Tc) capable of recognizing the antigen [1-3, 6]. As previously reported, the activated mDC are large producers of IL-23, TNF- α and IL-12. In the lymph node, these cytokines (along with other cytokines), lead naïve Th cells (Th0) of psoriasis patients to differentiate preferably in Th17, Th22 and Th1 [2, 3, 5, 6].

The activated Th and Tc leaves the lymph node expressing adhesion molecules (that fit the adhesion molecules expressed by activated endothelial cells on the skin) and access the dermis [1-2]. The Tc go to the epidermis and the Th concentrate in the dermis [1-3, 5]. The Th17, Th22 and Th1 now recognize the Ag in the dermis, interacting with the dermal Antigen-Presenting Cells (APC), i.e. CDm and macrophages [1, 2]. The APC are sources of IL-23, TNF- α and IL-12, cytokines that are respectively essential to Th17, Th22 and Th1 to proliferate and produce their specific repertoires of cytokines [1-6]. The Th17 lymphocytes are sources of IL-17, TNF- α , IL-6, IL-21 and IL-22. The Th22 produce IL-22 and TNF- α and the Th1 produce TNF- α and INF- γ (Figure 2) [1-6]. Cytokines from these Th (Th17, Th22 and Th1) act on keratinocytes, stimulating directly or indirectly their proliferation and the production of numerous proteins (cytokines, chemokines and AMP), perpetuating the inflammatory process (activating IIS and AIS cells and recruiting more cells of the IIS and the AIS to the skin) [1-6]. Among these cytokines, stand out IL-17, TNF- α , IL-22 and IFN- γ , acting individually and synergistically activating the transcription of numerous genes in the keratinocytes [2, 4-6].

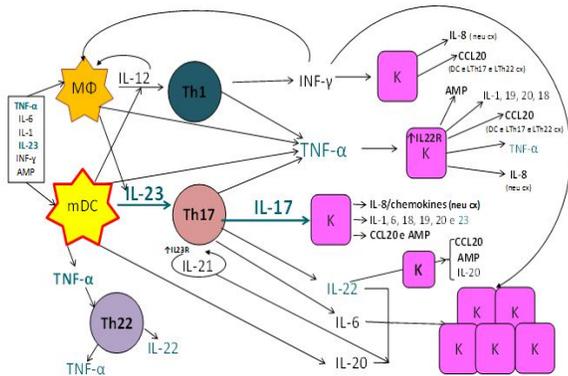


Figure 2: Immunopathogenesis of psoriasis: major proteins produced by myeloid dendritic cells (mDC), antigen presenting cells (APC) for macrophages (M ϕ), T-helper cells (Th) and keratinocytes (K). IL:interleukin; TNF- α : tumoral necrosis factor alpha; INF- γ : gamma interferon; AMP: antimicrobial peptides; CCL: chemokine. Th: T helper lymphocytes; DC: dendritic cell; R: receptor; HSP: heat shock proteins; neu: neutrophils; cx: chemotaxis.

The IL23 / IL-17 axis is the protagonist of the immunopathogenesis of psoriasis [2, 4-6]. It is noteworthy that IL-17 is produced not only by T17 cells (Th17 and Tc17) in psoriasis, but also by γ δ T cells and other IIS cells (neutrophils, mast cells and innate lymphoid cells) [2, 3, 5, 9, 10]. In addition, IL-23 appears

to affect the release of IL-17 by these IIS cells [2, 4, 5, 9].

Keratinocytes are the principal target for IL-17 (also known as IL-17A) in psoriasis. IL-17A stimulates keratinocyte expression of multiple chemokines for neutrophils: CXCL1, CXCL2, CXCL3, CXCL5 e CXCL8 (IL-8). [1-6]. In psoriasis skin lesions, neutrophils are potential sources of IL-17, they concentrate in the epidermis and appear to play an important role in maintaining the inflammatory process [2, 4, 6, 10]. Secukinumab (inhibitor of IL-17A) quickly causes the disappearance of neutrophils of the skin [10]. The inhibition of IL-17 by this biologic would reduce the production of chemokines by keratinocytes and therefore the arrival of neutrophils in the epidermis [10]. The disappearance of neutrophils correlated with the decrease in proliferation of keratinocytes, demonstrating a strong interaction between these IIS cells in the immunopathogenesis of psoriasis [10].

It is important to point out that IL-23 stimulates the mDC to produce TNF- α and that TNF- α stimulates the mDC to produce IL-23 [3-5]. Incidentally, the main therapeutic mechanism of action of anti-TNF in psoriasis seems to be just the decreased activation of mDC [5, 6].

Finally, psoriasis pathogenesis includes both innate and adaptive immune cells that interact with tissue cells producing large amounts of cytokines that, in turn, create reverberating inflammatory and proliferative circuits. Moreover, recent data point out the possibility that regulatory T lymphocytes of psoriasis patients could differentiate in vivo into Th17 cells, under proinflammatory conditions [11].

4 Conclusion

In conclusion, the knowledge of the main cells and cytokines involved in the immunopathogenesis of psoriasis is essential for dermatologists to understand better the disease as well as the mechanism of action of the biologics, drugs that revolutionized the treatment of psoriasis in the last two decades.

5 References

- Sanchez APG. Immunopathogenesis of psoriasis. *An Bras Dermatol*.2010;85(5):747-749.
- Di Meglio P, Perera GK, Nestle FO. The multitasking organ: recent insights into skin immune function. *Immunity*. 2011;35(6):857-869. doi: 10.1016/j.immuni.2011.12.003.
- Sweeney CM, Tobin A, Kirby B. Innate immunity in the pathogenesis of psoriasis. *Arch Dermatol Res*. 2011;303(10):691-705. doi: 10.1007/s00403-011-1169-1.
- Lynda Grine L, Dejager L, Libert C, Vandenbroucke RE. An inflammatory triangle in psoriasis: TNF, type I IFNs and IL-17. *Cytokine Growth Factor Reviews*. 2015;26(1):25-33. doi: 10.1016/j.cytogfr.2014.10.009.
- Yaxiong Deng Y, Chang C, Lu Q. The inflammatory response in psoriasis: a comprehensive review. *Clinic Rev Allerg Immunol*. 2016;50(3):377-389. doi: 10.1007/s12016-016-8535-x.

6. Lynde CW, Poulin Y, Vender R, Bourcier M, Khalil S. Interleukin 17A: toward a new understanding of psoriasis pathogenesis. *J Am Acad Dermatol*. 2014;71(1):141-150. doi: 10.1016/j.jaad.2013.12.036
7. Fry L Baker BS, Powles AV, Fahlen A, Engstrand L. Is chronic plaque psoriasis triggered by microbiota in the skin? *Br J Dermatol*. 2013;169(1):47-52. doi: 10.1111/bjd.12322
8. Arakawa A, Siewert K, Stöhr J, Besgen P, Kim SM, Rühl G, et al. Melanocyte antigen triggers autoimmunity in human psoriasis. *J Exp Med*. 2015;212(13):2203-2212. doi: 10.1084/jem.20151093
9. Lin AM, Rubin CJ, Khandpur R, Wang JY, Riblett M, Yalavarthi S, et al. Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis. *J Immunol*. 2011;187(1):490-500. doi: 10.4049/jimmunol.1100123
10. Reich K, Papp KP, Matheson RT, Tu JH, Bissonnette R, Bourcier M, et al. Evidence that a neutrophil-keratinocyte crosstalk is an early target of IL-17A inhibition in psoriasis. *Experimental Dermatology*. 2015;24(7):529-535. doi: 10.1111/exd.12710
11. Mattozzi C, Salvi M, D'Epiro S, Giancristoforo S, Macaluso L, Luci C, et al. Importance of regulatory T cells in the pathogenesis of psoriasis: review of the literature. *Dermatology*. 2013;227(2):134-145. doi: 10.1159/000353398