Chapter 5

Psoriatic Animal Models Developed for the Study of the Disease

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Abstract

Psoriasis is a skin disease mainly developed in humans, although it is also seen in monkeys and dogs. Animal models with psoriasis-like lesions have been a key factor for its understanding. Xenotransplants of human psoriatic skin in immunodeficient mice were the first approach for the association of immunologic problems with the development of psoriasis and have been also useful for the evaluation on new therapeutic agents. Imiquimod-induced murine psoriasis is nowadays one of the most used animal models to study this disease, perhaps because healthy wild-type mice are used, which means that it is an affordable model, easy to generate, and, more importantly, resembles the inflammatory, angiogenic and hyperproliferative characteristics of human psoriasis. Several transgenic (over-expressing VEGF, Tie2, TGFβ, STAT3, IL-36, PPARβ/γ) and knockout (lacking IκBα, JunB, IFNR-2, IL-36RA, CD18, IKK2) mice have been useful for the association of specific molecules for the development of psoriasis. Other approach has been the use of both transgenic/knockout mice and imiquimod treatment, where the importance of βTrCP, IκBζ, IL-35 and Tnip1 for the development of psoriasis was found. In this chapter, some of these animal models are discussed.

Keywords: psoriasis, animal models, skin immunology, angiogenesis, keratinocytes

1. Introduction

Psoriasis is a disease that has been accompanying the existence of humans. The ancient Greeks described an illness that seems to be psoriasis, but it could be confused with leprosy or Hansen's disease [1]. Because psoriasis develops naturally in humans but rarely in other species [2, 3], the

study of this disease was possible only after progress was made on immunology and on genetic engineering knowledge. Although reports on animals with psoriatic lesions due spontaneous mutations exist, the phenotype does not completely resemble human psoriasis, as occur with the homozygous asebia (Scd1ab/Scd1ab) mutant mice, the Flaky skin mice (Ttcfsn/Ttcfsn) and the spontaneous chronic proliferative dermatitis mutation mice [4, 5]. Now, with the advances on genetic engineering, some transgenic animals and animals with targeted mutations (knockout and knock-in) have been developed to study psoriasis. In the case of knockout models, the targeted gene is inactivated and the phenotype is caused by the absence of the targeted gene product. In the case of knock-in model, the gene is modified through targeted point mutation, with the addition or deletion of a nucleotide, instead of complete disruption of the target gene expression, and the phenotype depends on the expression of modified gene products. Knockout and knock-in animals are also developed with the use of tissue specific promoters to eliminate or express the targeted gene, and even more, the expression or suppression of the gene could be controlled by specific promoter regulators, where antibiotics and hormones are frequently used [6].

Another strategy to study psoriasis and other dermatologic illnesses in vitro is the development of 2nd- or 3rd-dimensional cell co-cultures. These systems have the limitation that so far has not been possible to include all the cellular types that are part of the skin, but have been very useful to evaluate new drugs for treatment [7].

2. Immunological factors in psoriasis

2.1. Humanized animal models (xenotransplantation)

Xenotransplantation was the first approach generated as animal model for the study of psoriasis and for the evaluation of anti-psoriatic treatments that consists in the transplantation of human skin in the back of inmunodeficient mice. In 1994, the first murine psoriasis model done in mice with severe combined immunodeficiency (SCID) was described. These mice have the so-called scid mutation that affects the "protein kinase DNA activated catalytic polypeptide" (Prkdc/DNA-PKcs), causing a defect in the antigen receptor gene rearrangement of lymphocytes, and consequently a SCID of the T- and B-cell systems [8]. In these mice, the psoriatic phenotype is kept for 2 months, enough time for the analysis of the disease. Later, it was demonstrated that mice with non-psoriatic human skin transplants that received lymphocytes from the psoriatic skin developed psoriasis; these facts demonstrated the importance of the immunologic factor for the development of this disease [9]. Also, the so-called nude mice are used to study psoriasis; these mice have a mutation in the forkhead box transcription factor N1 that results in defective thymus development, and therefore in lack functional T cells, or nude mice that lack recombinase activating genes 1 (Rag1) and 2 (Rag2) involved in the development of T and B cells.

2.2. Imiquimod-induced murine psoriasis (IMQ-Mu-Pso)

This transient model of psoriasis-like disease was developed by Van der Fits et al. [10], using non-genetically modified healthy mice daily treated with topic imiquimod or resiquimod (TLR7-TLR8 ligand) for 6 days. This simple model shows wide characteristics described in the human psoriatic

skin lesions, including: activation of pDC, Th17 cells producing IL-17, IL-22 and IL-23, activation of angiogenic process and hyperproliferacion of keratinocytes. IMQ-Mu-Pso model is generated due to an acute inflammation in the epidermis induced by imiquimod, hyperactivating the innate immunity and leading the adaptive immunity to produce great amounts of IL-17. IL-17, in turn, induces angiogenesis and proliferation of keratinocytes, as biological characteristics of psoriatic lesions. IMQ-Mu-Pso also demonstrated that undisrupted molecular and cellular mechanisms are able to break inflammation, as mice used for this model are healthy mice that show the highest production of inflammatory cytokines on the third day of treatment and show the highest development of psoriatic skin on the sixth day, but after this time, the mice are able to revert the inflammatory process as they are not genetically compromised. The short lasting presence of psoriatic lesions is an inconvenience of this model, although it has been widely used to elucidate the pathogenesis of psoriasis, and very interesting data have been published [10].

2.3. Intestinal microbiome affects the induction of psoriasis

The absence of 100% concordance between monozygotic twins suggests a crucial role of environmental factors for the development of psoriasis, as only 35–75% of monozygotic twins develop psoriasis; alcohol intake and smoking are considered non genetic factors that predispose individuals to develop psoriasis [11]. Intestinal microbiota has an important effect on the development and function of the immune system, for instance, a specific subset of microbiota has been shown to play roles in the development of Th17, meanwhile other subset favors the development of Treg cells [12]. Another study showed that microbiota from skin of psoriatic patients is different from healthy subjects; *Proteobacteria* were present at significantly higher levels in the psoriatic skin compared to limb skin used as control (52 vs. 32%, $p = 0.0113$), and in the same study, both *Staphylococci* and *Propionibacteria* were significantly lower in psoriasis versus control ($p = 0.051$, 0.046, respectively) [13]. In 2015, Zanvit et al. demonstrated that psoriasis is mediated by the early interaction between certain subset of bacterial microbiota and cells of immune system [14]. They treated 4-week-old mice with oral antibiotics (vancomycin and polymyxin B) showing a decrease in the severity of psoriasis compared to mice without antibiotics using the IMQ-Mu-Pso model. IL-17+ and IL-22+ T cells were significantly decreased in skin and gut in the antibiotic-treated mice; however, the Foxp3+ Treg cells were significantly increased in the skin of these mice. In contrast, when neonatal mice received the antibiotic treatment and the psoriasis was induced with imiquimod as 4-week old, they observed an increase in the severity of disease compared to mice without antibiotic treatment evidenced by the presence of immunological cells infiltration and by the increase of thickness in dermis; besides they did not find augment of IL-17+ cells, but significant increase of IL-22+ cells. The intestinal microbiota was also considerably different between mice treated with antibiotics as adults from those treated as neonates [14]. These results settle that among the factors that predispose to psoriasis is intestinal microbiota that depends on breast feed as neonates, type of food intake, but also on the use of antibiotics.

2.4. Disruption of NFκB and AP-1 to generate psoriasis in animal models

Innate immunity in skin is mediated by the activation of membrane receptors expressed on dendritic cells, Langerhans cells and macrophages activated by pathogens- or damage-molecular patterns (PAMP or DAMP). After ligand-receptor interaction, molecular signaling events

occur into the cell leading to the activation of transcription factors, such as NFκB and AP-1 that translocate into the nucleus for the expression of cytokines and antimicrobial peptides [15]. The malfunctioning in the regulation of the activity of these transcription factors could lead to the development of psoriatic lesions, as we next describe.

In unstimulated cells, NFκB dimers are sequestered in the cytoplasm by a family of inhibitors called IκB (Inhibitor of κB), and the IκB proteins mask the nuclear localization signals (NLS) of NFκB proteins and keep them sequestered in an inactive state in the cytoplasm. Activation of NFκB is initiated by the signal-induced degradation of IκB proteins; this occurs primarily by the activation of a kinase called IκB kinase (IKK). When activated by PAMPs or DAMPs, IKK phosphorylates two serine residues located in IκBα's regulatory domain, and then IκBα is ubiquitinated and degraded by the proteasome. With the degradation of IκBα, NFκB dimer is freed to enter into the nucleus to initiate the expression of specific genes that have DNA-binding sites for NFκB at their promoter site. The transcription of the targeted genes initiates a physiological response, for example, inflammation, cell survival and cellular proliferation. In fact, NFκB turns on the expression of its own repressor, IκBα. The newly synthesized IκBα then inhibits NFκB activity controlling the function of NFκB in an oscillatory way [15].

In IMQ-Mu-Pso, the severity of psoriatic lesions has been associated with a reduced presence of IκBα due over-degradation and in consequence with an enhanced NFκB activation. IκBα knockout mice developed psoriasis and died within the 7th–10th day after birth. The histological analysis showed myelopoietic tissues enlarged and diffusely distributed, and also alterations in the liver with enhanced splenic extramedullary hematopoiesiswith increased presence of monocytes/macrophages was seen [16].

"β-transducin repeat-containing protein" (β-TrCP) serves as substrate recognition component of E3 ubiquitin ligase that control the stability of important regulators of signal transduction, including IκBα. Mice with down-regulation of βTrCP ameliorate IMQ-Mu-Pso skin lesions, as IκBα does not degrade, keeping NFκB into the cytoplasm. This interesting finding suggests that βTrCP could be a novel target for developing agents to treat psoriasis, since it is involved in the NFκB signaling to regulate inflammation [17].

IκBζ is another molecule that interacts with NFκB, but inside the nucleus. This molecule has been recently identified as a key regulator in the development of psoriasis [18]. IκBζ is increased in psoriatic skin compared to non-psoriatic skin from the same patient. Some studies suggest that IκBζ associates with NFκB p50 subunit and binds to specific IκBζ response elements located in the promoter region of targeted genes consisting of NFκB- and C/EBP (CCAAT/enhancer-binding protein)-binding sites and exerts its transcription-enhancing activity on secondary response genes primarily by chromatin remodeling [19]. IκBζ is expressed in human keratinocytes induced with IL-17 and is a direct transcriptional activator of TNFα/IL-17-inducible psoriasis-associated proteins such as IL-8, IL-17C, IL-17A22, IL-19, IL23, IL22, CCL20 and hBD220. Interestingly, in imiquimod-treated IκBζ-deficient mice, psoriatic skin is not observed, and the molecules induced by TNFα/IL-17 are significantly down-expressed [20].

The dysfunctional activity of other transcription factors, for instance, AP-1 and STAT3, also contributes to skin inflammation development [21]. Mice with deficient expression of JunB and c-Jun, and mice with over-expression of FOS, generate a phenotype resembling the

histological characteristics of psoriasis, including the production pro-inflammatory cytokines. Besides, JunBexpression is reduced in epidermal keratinocytes of psoriatic patients in comparison with cells from healthy subjects [21]. Moreover, STAT3 transgenic mice and SOCS3 knockout mice (the negative regulator of STAT3) have constitutive activation of STAT3 and both develop murine IL-6-driven psoriasis [22, 23].

2.5. The role of cytokines in psoriasis

Other sort of psoriatic animal models includes those where cytokines and cells of immune system are involved. The importance of type I interferons in the psoriasis was demonstrated in "IFN regulatory factor-2" (IFNR-2)-deficient mice, a transcriptional repressor for IFN-$\alpha\beta$ signaling. These mice developed skin lesions similar to human psoriasis [24], in fact, type I interferons promote the activation of dermal dendritic cells (dDCs) [25].

Another cytokine with importance for the development of psoriasis is IL-36, an IL-1 family sub-member. The over-expression of IL-36α in transgenic murine (K14/IL-36) keratinocytes promotes acanthosis, hyperkeratosis, cells infiltration and increased expression of cytokines and chemokines [26]. The deficiency of IL-36RA (the natural antagonist of IL-36) in IL-36α (K14/IL-36, IL-36RA$^{-/-}$)-transgenic mice exacerbates the severity of psoriasis; histological analysis reveals intracorneal and intraepithelial pustules, parakeratotic and orthokeratotic hyperkeratosis, dilated superficial dermal blood vessels, and dermal inflammatory infiltrate. Additionally, mice deficient to IL-36 or in its receptor IL-36R are protected from IMQ-Mu-Pso [26]. In turn, IL-1β, TNFα, and IL-36 activate dDC and induce the production of IL-23, necessary for naive T cells to polarize to Th17, suggesting that IL-23 could be the link between the innate and adaptive immune response that occur in psoriasis [27]. In fact, it is possible to obtain psoriasiform skin in wild-type mice with nothing more but the inoculation of recombinant IL-23 or IL-17 [28]. In contrast, IL-35 has a potent immunosuppressive effect on HaCaT keratinocytes treated with TNF-α and IL-17 suppressing the expression of IL-6, CXCL8, and S100A7 [28]. In IMQ-Mu-Pso and K14-VEGF transgenic mice model, IL-35 reduced M1 macrophages (F4/80+CD80+), whereas anti-inflammatory M2 macrophages (F4/80+CD206+) were increased in the spleen and ear. IL-10–secreting CD4+, FoxP3+, CD25+ T cells were increased in those tissues, although IL-10–secreting CD25-T cells were also increased [29]. These results suggest that IL-35 treatment for psoriasis increases M2 macrophages as well as IL-10 production but suppresses Th17 cells development, consistent with the effect of IL-35 on Treg expansion, although not all IL-10 was secreted by Treg cells.

2.6. Cellular immunology in psoriasis

The insufficient regulation of specific cellular immune response is also involved in the development of psoriasis [30]. In normal conditions, Treg cells regulate the activity of auto-reactive Th1 and Th17 cells, but in psoriasis Treg cells might not be functional, as was evidenced in the CD18hypo mouse model [31]. Homozygous PL/J CD18 hypomorphic (CD18hypo)-mice developed spontaneously psoriasis-like skin in 12- to 14-week-old mice. CD18 is a molecule that together with CD11a constitutes an adhesion molecule of the β2 integrin family, important for the complete function of Treg cells. It has been suggested that CD18hypo mice induce psoriasis because CD18-low expressing Treg cells, or with a not fully active molecule, cannot

regulate the activity of auto-reactive Th1 and Th17 cells, since these mice improve when Treg cells from normal mice are transferred [32]. In CD18hypo mice, psoriatic lesions meliorate when macrophages are eliminated by the use of clodronate liposomes in the skin [33]. These results show the importance of Treg cell and macrophages in the evolution of psoriasis.

2.7. Implantable synthetic cytokine-converter cells model

Schukur et al. [34] designed the so-called implantable synthetic cytokine converter cells system based on the observation that psoriatic patients have high concentrations of TNFα and IL-22, and on the fact that IL-4 and IL-10 cytokines have an important anti-psoriatic effect. Considering the previous, they generated by genetic engineering human cells to react to high concentrations of TNFα and IL-22; these cells would be implanted to psoriatic patients and activated by TNFα and IL-22 from a psoriatic flare, and as a result, they would produce therapeutic doses of IL-4 and IL-10 to control inflammation. To achieve the goal, HEK-293T cells were co-transfected with the plasmids pNFκB-hIL-22RA-pA, phCMV-hSTAT3-pA, pSTAT3-mIL-4-pA and pSTAT3-mIL-10-pA. The authors first confirmed that co-transfected cells produced important levels of IL-4 and IL-10 when stimulated with TNFα and IL-22 in vitro [34]. TNFα activated the production of IL-22 receptor, and in turn IL-22 activated STAT3 signaling to induce the production of IL-4 and IL-10, to generate an anti-inflammatory environment. When co-transfected HEK-293T cells were intraperitoneally implanted into mice with IMQ-Mu-Pso the cytokines associated with the pathogenesis of psoriasis, such as IL-17, IFNα and C-X-C motif chemokine 9 (CXCL9), decreased substantially and a considerable increase in the production of the anti-inflammatory cytokines IL-4 and IL-10 was observed on day 5. Only the skin of animals with implanted co-transfected cells containing the antipsoriatic cytokine converter showed reduced skin lesions, evidenced by the reduction of erythema, scaling, and thickening. This is an interesting approach to treat psoriasis, although the complexity relies on the requirement to co-transfect cells from every single patient to avoid transplant rejection. Meanwhile, this system was also evaluated in vitro using blood from psoriatic patients and from healthy individuals, and interestingly only in blood from psoriatic patients increased levels of anti-inflammatory cytokines were detected [34].

3. Angiogenic factor in psoriasis

The altered function of angiogenic molecules also produces psoriasis. “Vascular endothelial growth factor” (VEGF)-transgenic mice [35], “endothelial specific receptor tyrosine kinase” (K5-Tie2)-transgenic mice [36], and “transforming growth factor beta 1” (K5-TGFβ1)-transgenic mice [37] are psoriasis animal models that highlight the importance of angiogenesis in this pathology. VEGF is a crucial factor that mediates the angiogenesis of blood vessels and is highly expressed in the psoriatic skin lesions. VEGF induces microvascular alterations in the dermal papillae, which facilitate the development and persistence of the psoriatic lesions [35]. Moreover, the increased vasculature and permeability provide nutrition to the hyperproliferating keratinocytes and promote the migration of inflammatory cells. The 6-month- old

K14-VEGF mice develop psoriasis, but if these mice are treated with imiquimod at 8-week old, the skin thickens, chemokines CXCL-9/10, CCL-20 and CCR6 increase, cytokines IL-23, IL-17, TNFα, and (IFN)-γ rise, and the cells CD11c+ DCs, Th17, Th1, $\gamma\delta$-T increase. In wild-type mice IMQ-Mu-Pso skin lesions last until day 7 of treatment, but in K14-VEGF mice treated with imiquimod, all the parameters described above are stable until day 14 [38]. This combined model IMQ-K14-VEGF is more appropriate for long-term studies compared to IMQ-Mu-Pso model, which is only an acute chemical-stimulated model.

Tie2 is the angiopoietin receptor that together with VEGF is essential for proliferation, maturation and for the maintenance of blood vessels. Hyperproliferation of keratinocytes and abundance of immunological cells infiltration, including Th17 cells, are detected in psoriatic skin. The over-expression of VEGF is promoted by TGFβ but also can be regulated by HIF-1α, as it is over-expressed in the psoriatic skin [36].

4. The role of keratinocytes in psoriasis

4.1. PPAR β/δ

The "peroxisome proliferator-activated receptor" (PPAR β/δ) transgenic mice, and the human keratinocytes autocrine growth factor (amphiregulin) transgenic mice [39, 40] both resemble psoriasis because they participate in the proliferation and differentiation of keratinocytes [41]. PPAR β/δ receptor is induced by TNFα, contributes to STAT3 phosphorylation, blocks apoptosis in keratinocytes, induces angiogenesis, and is up-regulated in human psoriatic skin [42]. In fact, PPAR β/δ directly induces the differentiation of keratinocytes, and in the transgenic mouse model, a light augment of Th17 is observed [43].

4.2. NFκB inhibits proliferation in keratinocytes

Genome-wide association studies suggest a link between psoriasis and the NFκB pathway, and this proposal has been supported by mouse models. Evidence gathered from diverse studies has shown that NFκB has a growth inhibitory function in the skin. Mice with epidermis-specific deletion of IKK2 (which mediates canonical NFκB activation) develop severe inflammatory skin disease that is mediated by TNFα, suggesting the critical function of IKK2-mediated NFκB activity in epidermal keratinocytes to regulate mechanisms that maintain the immune homeostasis of the skin [44].

Grinberg-Bleyer, et al. [45] described a murine psoriasis model that lacks the expression of p65 and c-Rel in epidermal cells. After birth, these mice developed severe psoriasis; early lesions were well-demarcated, scattered and rigid, with scaly plaques without edematous or exudative reaction aspect. H&E staining revealed epidermal thickening, hyperkeratosis and focal parakeratosis, as well as mononuclear infiltrates in the epidermis, which are features of psoriatic lesions. In this model, psoriatic lesions were resolved 30 days after birth by Treg cells effect, but when these cells were eliminated by the use of anti-CD25 antibodies, the deficient

mice showed a worsened pathology and the psoriatic lesions were reversed with anti-TNFα treatment [45]. Also RelA has a growth-inhibitory role in keratinocytes and prevents their differentiation [46]. Together, these results indicate that activation of canonical NFκB pathway in keratinocytes is required for their optimal differentiation and for the maintenance of immune homeostasis in the skin.

4.3. Prokineticin 2

Prokineticin2 (PK2), also named Bv8, is a small 8 KDa protein found in serum and dermis of psoriatic patients. PK2 participates in numerous important physiological processes including inflammation, neurogenesis, tissue development, angiogenesis, and even nociception [47, 48]. This peptide is mainly expressed in brain but can also be found in skin, bone marrow, lymphoid organs, granulocytes, dendritic cells and macrophages [49]. He et al. [50] found that bacterial products, including LPS and DNA, promoted in macrophages the production of PK2 and inflammatory factors, suggesting that infection is a primary inducer of PK2. The authors demonstrated that in macrophages PK2 induced high production of IL-1β, and in keratinocytes and fibroblast co-cultures PK2 induced IL-6, IL-8 and GM-SCF. In vivo PK2 promoted the differentiation of fibroblast and keratinocytes [51]. Besides, when PK2 was over-expressed in psoriasis-K14-VEGF transgenic mouse model, psoriatic lesions were gradually aggravated, as evaluated by increase of redness, swelling, weight, thickness, scaly epidermis, keratinocyte hyper-proliferation, and increase of IL-1β, TNFα, IFNγ, IL-12, IL-22, IL-23, IL-17 in the ear; moreover, increase of lymph node weight was also seen. On the contrary, in psoriatic-K14-VEGF transgenic mouse model with PK2 down-regulated, the psoriatic lesions were abrogated [50]. The results suggest that PK2 aggravates psoriasis by the promotion of keratinocytes and fibroblasts proliferation, inflammation, and angiogenesis.

4.4. Tnip1

The big dilemma about psoriasis is whether the root of the problem falls on keratinocytes or on immunological cells dysfunction. It has been well described that IL-23-producing myeloid cells and IL-17–producing T cells are abundant in psoriatic skin, and that IL-23 and IL-17 induce in keratinocytes and fibroblasts high production of chemokines, which in turn, recruit even more immunological cells creating a feedback loop that worsens the disease. In keratinocytes and immunological cells, "TNFAIP3-inter-acting protein 1" (Tnip1) down-regulates the chemokines production induced by IL-17 [50]. Ippagunta et al. [52], using the IMQ-Mu-Pso model under the Tnip-keratinocyte-specific-deletion mice (Tnip1flox/flox K14-Cre), found that keratinocytes contribute intrinsically to psoriasis because when keratinocytes lost Tnip1 function they could not control the production of chemokines induced by IL-17. Tnip1flox/floxK14-Cre mice developed severe psoriasis when low doses of imiquimod were used, even at concentrations on which WT mice do not develop psoriasis. Interestingly, when bone marrow cells from Tnip1-/- mice were transferred to WT mice and treated with low doses of imiquimod, they did not developed psoriasis, confirming that the lack of function of Tnip1 in keratinocytes and fibroblast, but not in hematopoietic lineage cells, generate

psoriasis [52]. With these results, the authors provide evidence that specifically skin-resident keratinocytes contribute causally to psoriasis.

5. In vitro models for the study of psoriasis

As we previously mentioned, animal models have been very useful to dissect the molecular and cellular mechanisms for psoriasis development. These models have been also advantageous to evaluate new pharmaceuticals, nevertheless the physiology, anatomy and molecular differences between animal models and humans cause that only around 10% of new treatments assayed on phase I, be really useful in humans [53]. Although humanized models have also been developed, immunodeficient animals are most commonly used. Alternative methods have been developed to analyze the effect of new anti-psoriatic drugs; 2D, 2D+membrane, and 3D cell cultures have been designed [54]. 2D model consists of primary explants of keratinocytes or fibroblasts from psoriatic patients cultured over extracellular matrix proteins to evaluate cellular proliferation, cellular differentiation and cytokines production [55]. In the 2D+membrane model, two cell types are co-cultured separated by a synthetic membrane to evaluate the interconnection between two cell types in the pathology [56]. 3D cultures, also known as organotypic culture system (OCS), allow the growth of complex biological systems in vitro in a way that resembles part of their normal physiology and function. OCSs are powerful as experimental platforms in preclinical dermatological research, helping to validate mechanisms of diseases and to test the therapeutic potential of candidate drugs [57]. The new generation of 3D cultures connected to biosensors or chips allows real-time monitoring of biological parameters such as loss of water and electrophysiologic parameters [58].

6. Conclusion

The actual hypothesis about the cellular and molecular mechanisms that lead to the development of psoriatic lesions has been established by the use of animal models. The use of xenotransplants confirmed the important role of immunology in this disease. The studies done in genetically modified mice that overproduce (transgenic) or lack (knockout) certain proteins reveal specific protagonists of innate or adaptive immunity, angiogenesis or proliferation for the development of psoriasis.

In **Figure 1**, we represent a developing inflammation mechanism generated in the skin of healthy individuals denoted as a brown cogwheel system, where a trigger induces the innate and adaptive immune response, and in turn angiogenesis and keratinocytes proliferation are activated. Every cog represents one participant in inflammation: cell (DCs, macrophages, iLC IL-17+, Th1, Th17, keratinocytes, between others) or molecule (TLRs, NFκB, βTrCP, IκBζ, Stat3, TNFα, IFNα, IL-12, IL-36, IL-23, Th1, IL-6, Th17, IL-17, CCR6, VEGF, Tie2 TGFβ1, PPAR$\alpha\beta$, PK2, between others). The red arrows indicate the movement of the cogwheels for the progression of inflammation. In healthy people, the inflammation is controlled by

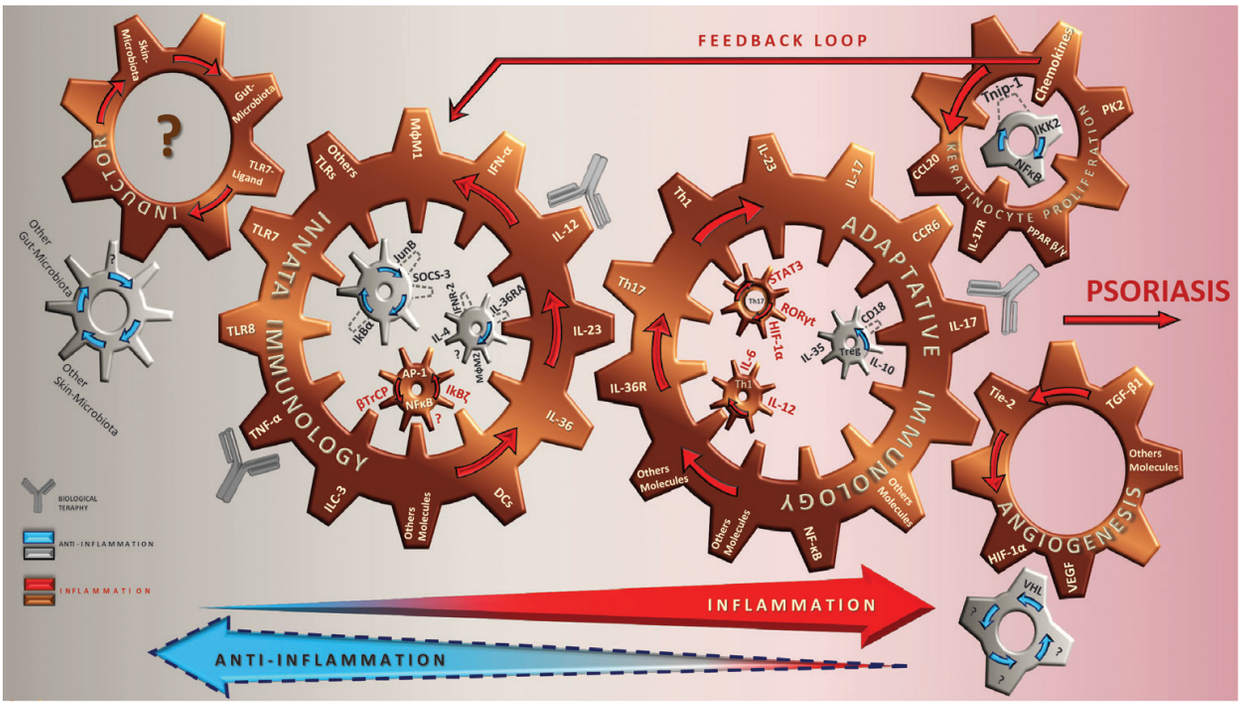

Figure 1. Inflammatory process. The developing inflammation mechanism generated in the skin is represented in this cogwheel system, where innate immune response, adaptive immune response, angiogenesis and cellular proliferation are represented in independent but interconnected cogwheels. Brown cogwheels represent inflammatory mechanisms moving in a pro-inflammatory sense (red arrows), where each cog represents one participant in inflammation (cell or molecule). Gray cogwheels represent the anti-inflammatory mechanism spinning the wheels in the opposite direction (blue arrows) to regulate inflammation. The "ghost" cogs (discontinuous lines) represent dysfunctional cells or molecules that disrupt effectiveness in the control of inflammation, favoring the development of psoriasis. Some antibodies interfere with the spinning of pro-inflammatory cogwheels, representing therapies with antibodies developed to control psoriasis. Question marks represent molecules to be discovered.

the activation of anti-inflammatory process after damage reparation. The cells (Treg and M2 macrophages) and molecules (IκBα, JunB, SOCS-3, IFNR-2, IL-36RA, IL-4, IL-10, IL-35, CD18, VHL, Tnip-1, between others) involved in the anti-inflammatory process are represented in the gray cogwheels. The blue arrows indicate the movement of the cogwheels for the progression of anti-inflammation. The "ghost" cogs (discontinuous lines) represent those dysfunctional molecules or cells that disrupt effectiveness in the control of inflammation, favoring the development of psoriasis.

Based on all the facts discussed in this chapter, we can conclude that psoriasis occurs in individuals with the anti-inflammatory regulation disrupted in immunological but also in non-immunological skin-resident cells.

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