Signalling in inflammatory skin disease by AP-1 (Fos/Jun)

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ABSTRACT

Skin inflammation is a physiological reaction to tissue injury, pathogen invasion and irritants. During this process, innate and/or adaptive immune cells are activated and recruited to the site of inflammation to either promote or suppress inflammation. The sequential recruitment and activation of immune cells is modulated by a combination of cytokines and chemokines, which are regulated by transcription factors, such as AP-1 (Fos/Jun), NF-κB, NFATs, and STATs.

Here we review the present evidence and the underlying mechanisms of how Jun/AP-1 proteins control skin inflammation. Genetically engineered mouse models (GEMMs) in which AP-1 proteins are deleted in the epidermis have revealed that these proteins control cytokine expression at multiple levels. Constitutive epidermal deletion of JunB in mice leads to a multi-organ disease characterised by increased levels of pro-inflammatory cytokines. These JunB-deficient mutant mice display several phenotypes from skin inflammation to a G-CSF-dependent myeloproliferative disease, as well as kidney atrophy and bone loss, reminiscent of psoriasis and systemic lupus erythematosus.

Importantly, epidermal deletion of both JunB and c-Jun in an inducible manner in adult mice leads to a psoriasis-like disease, in which the epidermal proteome expression profile is comparable to the one from psoriasis patient samples. In this GEMM and in psoriasis patient-derived material, S100A8/A9-dependent C3/CFB complement activation, as well as a miR-21*-dependent TIMP-3/TACE pathway leading to TNF-α shedding, plays causal roles in disease development. The newly identified therapeutic targets from GEMMs together with investigations in human patient samples open up new avenues for therapeutic interventions for psoriasis and related inflammatory skin diseases.*

Introduction

To better understand the pathogenesis of inflammatory skin diseases and develop innovative therapeutic approaches, it is essential to uncover the molecular mechanisms that underlie pro-inflammatory stimuli. The AP-1 transcription factor complex which has roles in cell proliferation, differentiation and cell transformation during development as well as in adult tissues, is also a key player in regulating inflammatory processes (1). AP-1 is composed of homo- and heterodimeric complexes consisting of members of the Jun, Fos, ATF (activating transcription factor) and MAF (musculoaponeurotic fibrosarcoma) protein families (2). AP-1 family of transcription factors can be activated by growth factors, cytokines, chemokines, hormones and multiple environmental stresses. For instance, activation of cascades involving the stress-responsive MAPKs (mitogen activated protein kinases), such as JNKs (Jun-N-terminal kinases), leads to activation of AP-1 (3). The regulation of AP-1 complexes can occur at several levels, including transcription, mRNA translation, turnover and protein stability. These processes can be regulated by microRNAs, or interactions with other transcription factors. Moreover, different AP-1 dimers are expressed in a cell- and stage-dependent manner (4). Over the past 20 years, genetically engineered mouse models (GEMMs) carrying specific genetic alterations of AP-1 genes have provided novel insights into their functions, in particular in bone, liver and skin biology. These studies have shown that AP-1 proteins are not only important regulators of tissue homeostasis, but also control important processes like cell proliferation, differentiation, apoptosis and inflammation. Recently, several reports demonstrated that AP-1 factors have important roles in common human diseases such as psoriasis, fibrosis and cancer (5-8). In this review, we summarise the

current knowledge on the role of Jun proteins in inflammatory skin diseases, discuss patient-derived xenotransplant (PDX) and Jun-dependent GEMMs for psoriasis and skin inflammation, and demonstrate their value for pre-clinical studies and therapeutic interventions.

Skin homeostasis and inflammation mediated by Jun/AP-1 proteins

The skin provides a protective barrier at the body's surface against infection by pathogens and other potentially dangerous events, such as injuries, UV-radiation and dehydration. The epidermis, which forms the outermost layer of the skin, is mainly composed of keratinocytes and undergoes continuous self-renewal. Skin homeostasis is maintained through a complex interplay of cytokines and growth factors, controlling the balance between proliferation, differentiation and apoptosis of keratinocytes. In the epidermis, AP-1 was shown to regulate a wide range of processes, including differentiation, carcinogenesis, UV response, photoaging and wound repair (2, 9). The majority of AP-1 members are constitutively expressed in the basal layer of the murine and human epidermis. While c-Jun is expressed in the basal and suprabasal cell layers of mouse epidermis, it is only detectable in the granular layer of human epidermis. On the contrary, JunB is expressed in all cell layers of both mouse and human epidermis (10). Fra-2 is also expressed in all layers of the mouse epidermis with highest expression in supra-basal layers. A GEMM with epidermal *Fra-2* deletion displays perinatal lethality with systemic inflammation as well as defects in terminal keratinocyte differentiation. We have recently demonstrated that this defect in epithelial differentiation is regulated by an interaction of Fra-2 with Ezh2 and Erk1/2 (11). Furthermore, Fra-2 controls skin inflammation by regulating p65/NF-kB-dependent and -independent inflammatory mediators. We were able to show a cell autonomous regulation of TSLP cytokine expression by Fra-2, which inversely correlates with the differentiation status of keratinocytes (unpublished data). Collectively, these findings identify an important function of epidermal p65 in initiating inflammatory processes and also reveal a central role of Fra-2 as a gatekeeper of barrier immunity.

Interestingly, tissue-specific loss-of-function studies in mice provide compelling evidence that AP-1 proteins are important regulators of skin inflammation and cytokine expression (5, 8, 12–15). Based on these discoveries, the mouse skin has become an essential model to study the function of Fos and Jun proteins in skin physiology and disease.

Constitutive loss of *JunB* in epithelial cells leads to a multi-organ disease

Altered *JunB* expression and/or activity were observed in psoriatic skin lesions (16-18). Therefore, deregulated JunB could be one initiating event in the etiology of inflammatory skin diseases. Interestingly, human *JunB* (19p13.2) is located in the psoriasis susceptibility region PSORS6 and down-regulation of JunB in the epidermis could serve as a contributing factor in psoriasis (8). Deletion of *JunB* in epithelial tissues ($JunB^{\Delta ep}$) leads to a multi-organ disease with skin ulcerations in the facial area, myeloproliferative disease (MPD) in the bone marrow, systemic lupus erythematosus (SLE)-like disease and bone loss (15, 19). This effect of epithelial *JunB* deletion on multiple organs is likely explained by increased expression of cytokines from JunB-deficient keratinocytes, which can initiate a pro-inflammatory cascade. G-CSF (granulocyte colony-stimulating factor), secreted by keratinocytes under the transcriptional control of JunB is mostly responsible for the skin inflammation as well as the MPD in these mice (15). Furthermore, increased expression of IL-6 (interleukin 6) is also observed in skin of $JunB^{\Delta ep}$ mice and appears to affect the kidneys leading to a SLE-like autoimmune disease in adult mutant mice (19). JunB directly binds to the promoters of G-CSF and IL-6 thereby inhibiting their expression (15, 19). Interestingly, when $JunB^{\Delta ep}$ mice are crossed with mice carrying deletions of these cytokines, the skin, kidney and MPD phenotypes are ameliorated (15, 19), indicating that JunB can act as a negative regulator of several cytokines in keratinocytes. Similarly, analyses of human skin biopsies from SLE patients revealed reduced JunB and elevated IL-6 protein levels, suggesting an essential role of JunB in the pathogenesis of human SLE (19). In summary, an epithelial deletion of JunB appears to affect processes in distant organs, such as myelopoiesis in the bone marrow and bone homeostasis (15). This supports the notion that JunB has an essential role in the endocrine-like function of the skin.

As deletion of *IL-6* and *G-CSF* in $JunB^{\Delta ep}$ mice led to a rescue of the skin, kidney and MPD phenotypes, but not the bone loss (15, 19), we hypothesised that there could be other unidentified soluble factors that are responsible for the cross-talk between skin and bone. Through a high-throughput screen of molecules in the serum of the $JunB^{\Delta ep}$ mice, we identified IL-17 (Interleukin-17), a pro-inflammatory cytokine mostly known to be produced by the T-helper cell subset Th17 cells (20, 21). We show that IL-17 is produced by a newly identified cell type called Innate Lymphoid Cell Group3 (22) together with γδT-cells in the skin of $JunB^{\Delta ep}$ mice (23-25). Crossing $JunB^{\Delta ep}$ mice to a lympho-deficient background using *Rag1*-/- mice, we demonstrate that IL-17 production from T-cells is dispensable for skin inflammation and bone loss.

IL-17 appears to be responsible for the decrease in bone mass by reducing the rates of bone formation with a dramatic reduction in the levels of the bone hormone osteocalcin (OCN), without obvious effect on bone degradation/resorption. Inhibition of IL-17 *in vivo* employing blocking antibodies is sufficient to rescue the bone loss. A direct action of this cytokine on bone forming osteoblasts and osteocytes is evident *in vivo* as well as *in vitro* cultures. Moreover, psoriasis patients with no arthritis show signs of bone loss with reduced levels of serum OCN and P1NP that correlate with the serum levels of IL-17 (ECTS Annual Meeting 2015 Uluçkan, Ö. *et al*. and unpublished results). These findings are of clinical relevance

as IL-17 blockade is currently approved as standard-of-care treatment in psoriasis patients (26). These results emphasise the important role of the skin as an endocrine organ and highlight JunB as a central transcription factor that not only controls skin homeostasis, but also regulates the cross-talk of skin to other organs, such as kidney and bone.

Inducible loss of *JunB* and *c-Jun* leads to a psoriasis-like disease

Psoriasis is a chronic recurrent disabling skin disease that affects approximately 2% of the population. Persistent plaques of inflamed and scaly skin characterise the prototypic form of psoriasis. The initial trigger(s) leading to the development of psoriasis are largely unknown, although much emphasis is currently placed on this relevant aspect. It has been demonstrated that both the innate and adaptive immune systems play important roles in the patho-physiology of psoriasis. Several mouse models of psoriasis, targeting either immune cells or keratinocytes have been developed, constituting powerful tools to dissect the underlying molecular mechanisms that trigger aspects of this disease (27, 28). When both Jun proteins are inducibly deleted in the epidermis of adult mice (DKO*), mutant mice develop a chronic psoriasis-like skin disease within two weeks (12). The phenotype of DKO* mice shares many key features with the symptoms observed in psoriasis patients, for instance inflammation of joints, hyper- and parakeratosis of the epidermis as well as epidermal infiltration of T cells and neutrophils (12). There is also accumulation of neutrophils in epidermal microabcesses (12). Furthermore, the cytokine profile is reminiscent of psoriasis and expression of Th17 cytokines is increased (20, 21). Moreover, a dermal increase in blood vessel density is also observed in these mice (29). We have investigated a possible beneficial outcome of an anti-angiogenic therapy, using an anti-VEGF antibody in the psoriasis-like mouse model. Systemic treatment of mutant mice with the anti-VEGF antibody in a therapeutic trial showed an overall improvement of the psoriatic phenotype with normalisation of the epidermal architecture and a reduction in the number and size of blood vessels. Moreover, the immune infiltrate in the skin was reduced, thereby proposing integration of anti-angiogenic therapy for the treatment of psoriasis (29).

Functions of S100 proteins in the pathogenesis of psoriasis

To validate the AP-1-dependent GEMM for psoriasis, we next sought to compare the signalling pathways activated/repressed in the mouse model and compare it to lesional skin from psoriasis patients. An unbiased iTRAQ proteomic screen of the epidermal compartments from psoriatic patients and GEMMs of psoriasis allowed us to uncover a functional link between S100A8/A9, which were identified as the top upregulated proteins in psoriatic epidermis, and the alternative complement pathway C3-CFB (8) (Fig. 1A). Furthermore, S100A8/A9 was found to bind to the C3 promoter region, thus highlighting a previously unknown nuclear function of S100A8/A9. Noteworthy, the secretion of S100A8/A9 and C3 by keratinocytes and binding to their corresponding receptors, *e.g.* RAGE (damage associated molecular pattern molecules) receptors or CD11b on infiltrating immune cells stimulates these to produce pro-inflammatory cytokines like IL-17, MCP-1 and RANTES. We propose that induction of C3 by S100A8-S100A9 can lead to "primed" keratinocytes and subsequently to uncontrolled immune cell activation, angiogenesis, hyperproliferation of keratinocytes and finally to the chronic inflammation that characterises psoriasis (8).

Importantly, we show that genetic deletion of S100A9 in the psoriasis-like mouse model reduced expression of complement factor C3 and its activation partner CFB as well as IL-1β, thereby preventing the psoriasis-like disease. In addition, blocking C3 in a mouse model attenuated the psoriasis-like phenotype. These results imply that S100A8/A9 and C3 are not only serum markers for psoriasis severity, but likely serve as important amplifiers in psoriasis patho-physiology (8).

Until now S100A8/A9 proteins were mainly considered as chemo-attractant proteins in mouse and anti-microbial in human. Our findings show that these proteins can be found in the chromatin enriched fraction in keratinocytes and can be implicated as modifiers of C3 transcription. It is not yet known how these proteins enter the nucleus, since no nuclear localisation signal has been reported. Our data indicate that the effect of S100A8/A9 on transcription is not achieved like a classical transcription factor, but rather through chromatin binding and remodelling. S100A8/A9 proteins interact in the nucleus with histones and nucleosomes, thereby likely inducing epigenetic changes in gene expression. Future work will explore this newly discovered and conceptually novel activity of S100A8/A9 as well as whether these findings are applicable to other S100 proteins and other cell types, such as neutrophils.

Role of miRNAs in the pathogenesis of psoriasis

Psoriasis is a complex inflammatory skin disease and its etiology is not well understood. It has been proposed that deregulation of miRNAs could be one underlying cause for psoriasis development. Several miRNAs were described to be upregulated in psoriasis (18, 30), but their causal contribution to disease development has not been demonstrated. The psoriasis-specific miRNA profile shows that *miR-203* levels are increased correlating with the down-regulation of SOCS-3 (suppressor of cytokine signalling 3), which is involved in inflammatory responses and keratinocyte functions. In a different study, *miR-221* and *miR-222* amounts are increased in psoriasis correlating with TIMP-3 down-regulation (18). Supporting evidence that TIMP-3 plays an important role in the patho-physiology of psoriasis comes from studies in the Jun/AP-1 psoriasis-like mouse model described above. In this mouse model, epithelial deletion of JunB and c-Jun leads to a down-regulation of TIMP-3, followed by an up-regulation of TACE activity resulting in dramatically increased soluble TNF-α levels (13). Interestingly,

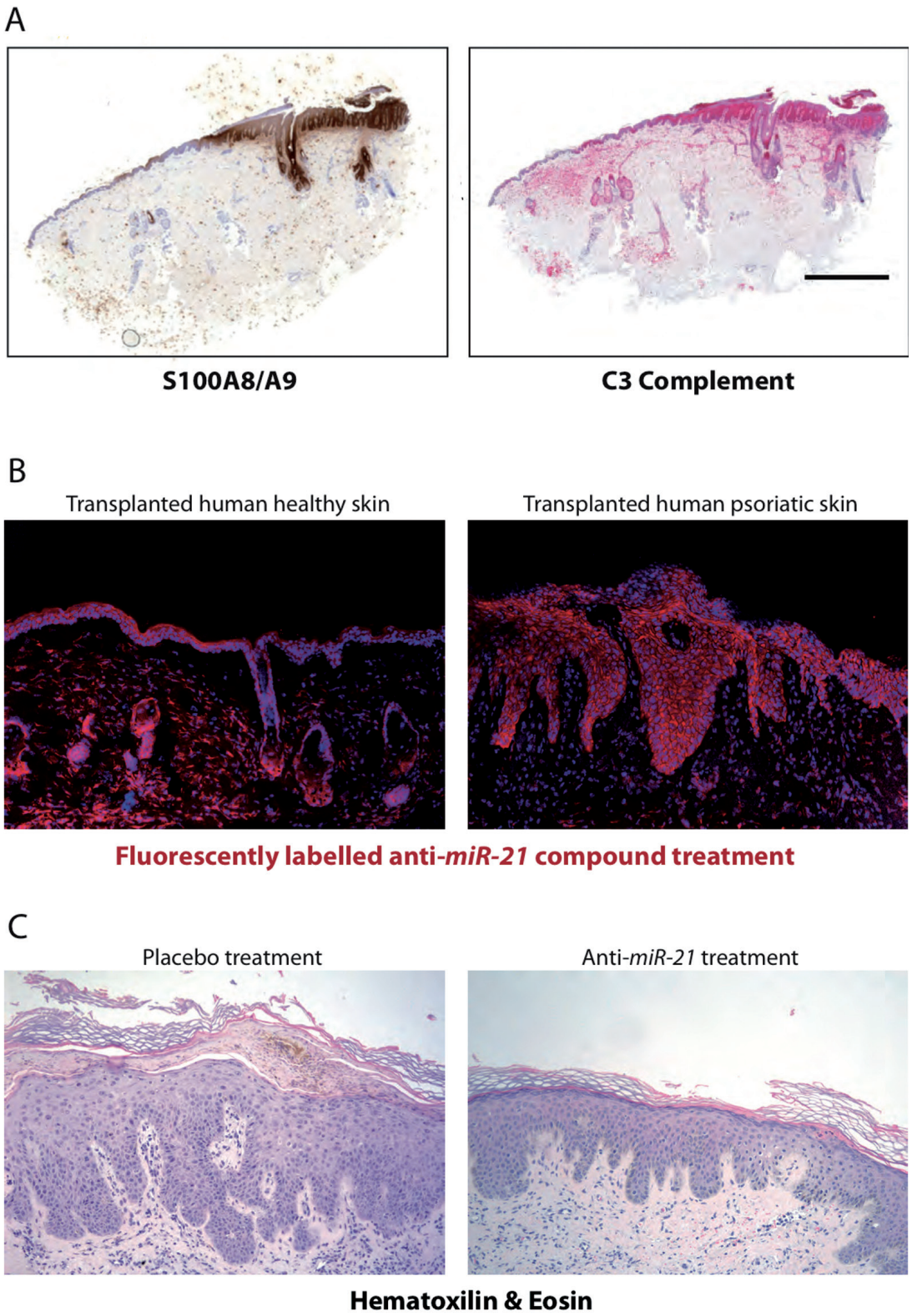

Fig. 1. A. Immunohistochemistry staining for S100A8/A9 and complement C3 factor in psoriasis biopsies spanning from non-lesional to lesional areas. Overlapping expression patterns of S100A8/A9 and C3 are detected in lesional areas. **B.** Immunofluorescence showing the distribution of fluorescently labelled anti-miR-21 compound upon intradermal injection in psoriasis patient-derived xenotransplants (PDX). **C.** Haematoxilin and Eosin staining showing reduced epidermal thickening upon miR-21 inhibition in psoriasis patient-derived xenotransplants (PDX).

miR-21, a known onco-miR (31) that targets TIMP-3, was also shown to be upregulated in psoriasis (32). We have recently shown that *miR-21* expression is increased in epidermal lesions of patients with psoriasis, as well as in the Jun/AP-1 psoriasis-like mouse model. Importantly, *miR-21* upregulation led to reduced epidermal TIMP-3 expression, activation of TACE/ADAM17 and increase in the TNF-α levels (7). Mechanistically, using patient-derived skin samples and the Jun/AP-1 GEMM of psoriasis, we were able to show that increased *miR-21* levels may be the result of impaired transcriptional activity of Jun/AP-1 and/or JunB downregulation, as has been reported for psoriasis

(2). We further show that JunB can inhibit IL-6 expression in keratinocytes and as a consequence the Stat-3 pathway is activated. Stat3 is a well-known transcriptional activator of *miR-21*. Using the epidermal-specific Stat3c transgenic mouse model, which develops a psoriasis-like phenotype, we observed that *miR-21* levels are increased in these mutant mice. Thus, we demonstrated that epidermal Stat3 induces the expression of *miR-21* and a psoriasis-like phenotype (7).

Given these findings, and the relevance of the *miR-21*/TIMP-3/TACE pathway linking to TNF-α shedding in psoriasis, we decided to antagonise these molecules *in vivo* to address if they are causal to disease development. Inhibition of *miR-21* by locked nucleic acid (LNA)-modified anti-*miR-21* compounds ameliorated disease pathology in patient-derived psoriatic skin xenotransplants (PDX) and in the Jun/AP-1 psoriasis-like GEMM (Fig. 1B,C). Importantly, when the beneficial outcome of targeting *miR-21* was compared to that for anti-TNF-α (Enbrel, Amgen), we observed identical efficacy. In addition, the therapeutic benefit of restoring TIMP-3 expression or targeting TACE in the Jun/AP-1 psoriasis-like GEMM was also demonstrated. Therefore, modulating *miR-21* and the downstream targets TIMP-3 or TACE may be a potential therapeutic strategy for treating psoriasis.

Novel therapeutic targets and future perspectives

In the last decade "biological therapies", which suppress inflammation through different means, have demonstrated to be effective, innovative treatments for inflammatory skin diseases. Nevertheless, a relevant concern is always the side effects of long-term chronic immune-suppression, which has been shown to increase the risk of infection and cancer (33). Thus, the development of efficient drugs lacking these side effects that could potentially be applied in a local manner would be beneficial for psoriatic patients. As S100A9$^{-/-}$ mice are viable and show no skin phenotype, blocking S100A9 in psoriatic patients might be beneficial without impairing skin function. The described S100A9 inhibitor Tasquinimod is currently being tested for the treatment of castration-resistant prostate cancer (34). Preclinical tests in the psoriasis mouse models should provide insights into its potential pharmacological effect in psoriasis and inflammation-mediated diseases. Interestingly, case reports have shown that targeting C3 can also be beneficial for psoriatic patient (28). In addition, immunoglobulin-based drugs which function as a sink for complement components, including C3 have emerged as effective long-term therapies in patients with autoimmune diseases (35). Therefore, inhibitory strategies for S100A8/A9 and/or C3 have exciting potential to become effective new therapeutics for psoriasis.

The therapeutic effects of targeting *miR-21* and the downstream TIMP-3/TACE/TNF-α axis should be tested in other subtypes of psoriasis, in addition to *psoriasis vulgaris*. Moreover, the beneficial outcome of targeting *miR-21* needs to be compared to new emerging therapies for psoriasis like anti-IL-17, anti-IL-17R, anti-IL-12/23 and anti-PDE4 inhibitors (33). Finally, systemic, intra-dermal and topical delivery of anti-*miR-21* oligos, TIMP-3 protein or TACE inhibitors will need to be thoroughly tested pre-clinically for safety and efficacy before moving towards clinical trials. Moreover, given the advances to target even transcription factors, it is worth considering the application of novel or already established inhibitors of AP-1 (Fos/Jun), as we have successfully shown in human SCC-cell lines (14).

Recently, several reports suggest that the balance between the host and the microbiome plays an important role in skin immunity (36-38). Skin-resident microbes have been associated with a variety of dermatological pathologies, such as AD, SLE and psoriasis (39). Some studies identified potential differences in the composition of the skin microbiota in psoriatic patients, although to date no consensus microorganisms have been linked to disease pathogenesis (39). Thus, it remains unclear how alterations in skin microbial communities and the intrinsic features of the host in psoriasis are connected and how this affects disease progression and local as well as systemic inflammation.

The physiological function of inflammation is to resolve injuries and/or remove pathogens from the body. However, if inflammation itself is not terminated, it can result in chronic inflammation that can lead to organ damage or diseases, such as psoriasis and several forms of inflammation-associated cancers. Understanding the molecular pathways leading to chronic inflammatory diseases is fundamental to develop more effective treatments. New studies will further investigate the underlying molecular networks and the role of these in controlling multiple and important pathways in inflammatory skin diseases. GEMMs will undoubtedly be refined and 'humanised', mainly focusing on improving the PDX-models, which would then also be employed for drug screening. It will be of high importance to analyse the role of the skin microbiota and manipulate this system by housing the GEMMs with skin inflammation in germ-free conditions, as well as transplant of specific types of microbes back to germ-free animals. Future progress will depend on a successful integration of novel GEMMs and innovative studies using human culture systems, transplantation approaches and patient analyses, including personalised large-scale "omic" approaches.

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