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REVIEW ARTICLE

Psoriasis and Psoriatic Arthritis: Flip Sides of the Coin?

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Presence (current or past) of psoriasis of the skin is a major criterion to establish the diagnosis of psoriatic arthritis. However, in individual patients, the course of psoriasis and psoriatic arthritis do not seem to correlate. This raises the issue of whether psoriasis and psoriatic arthritis are distinct entities, or parts of the spectrum of a "psoriatic disease". Arguments in favour of both concepts, derived from clinical observations, animal experiments, genetic approaches, and therapeutic studies are reviewed, and the implications for scientists and practicing dermatologists highlighted. ***Key words: psoriasis; psoriatic arthritis; genetics; animal models; pathogenetics; therapy.***

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Psoriasis (PsO) is a common skin disease, with a prevalence of approximately 2% in most populations studied so far. Its most typical manifestations are demarked, red, scaly plaques approximately the size of the palm of the hand. A number of important pathologies are observed more often than expected among patients with PsO, based on their respective prevalences. These so-called comorbid diseases include psoriatic arthritis (PsA), metabolic syndrome or components thereof, cardiovascular disorders, as well as numerous other diseases, such as anxiety/depression, non-alcoholic fatty liver disease, Crohn's disease, or lymphoma (1). Fifty years ago psoriatic arthritis was defined as a separate entity within the group of spondylarthropathies, comprising a wide spectrum of musculoskeletal manifestations (2). The association of PsO with PsA, in particular, is so important, that current or past presence of PsO, or a positive family history, represent key elements to establish the diagnosis of PsA according to the Classification of Psoriatic Arthritis (CASPAR) criteria, usually referred to when defining PsA (3). However, clinical experience seems to suggest that the course of PsO and PsA in individual patients do not correlate. Should we therefore consider them as distinct entities, or rather different manifestations of a "psoriatic disease"? This review discusses arguments in favour of both hypotheses, derived from numerous methodically distinct approaches, before addressing important implications for scientists and practicing dermatologists (Table I).

CLINICAL OBSERVATIONS

When considering PsO and PsA as flip sides of a coin, some physicians envision the image of corresponding tubes, with high activity on one side being linked to low activity on the other. Others argue in terms of a total inflammatory burden that is high during phases of exacerbation, but low during phases of remission or minimal disease activity, the latter being a general concept also put forward in the field of PsO and PsA (4).

An example of how a clinical manifestation of PsA could directly induce symptoms of PsO is nail psoriasis: enthesitis, i.e. inflammation at the bony insertion points of tendons, is a common clinical feature of PsA. Upon manifestation at the level of the distal interphalangeal joints, it affects the whole enthesis organ apparatus, comprising the dorsal capsular enthesis and the nail bed (5). Thus, typical signs of nail bed PsO, such as onycholysis or dystrophy, could be regarded as being related to enthesitis. It must be stressed, however, that enthesitis at the distal interphalangeal joints is not always associated with symptoms of the corresponding nail, and nail psoriasis is not always associated with enthesitis of the respective digit.

In contrast, numerous clinical observations suggest that the clinical course of PsO and PsA are not related to each other. When looking at the baseline characteristics of patients included in clinical studies for both indications, PsO trials tend to comprise patients with severe skin involvement and little joint symptoms, while the opposite is true for PsA trials. An example is the clinical development programme of the tumour necrosis factor alpha (TNF-α) inhibitor infliximab, with patients enrolled in the PsO study EXPRESS exhibiting a mean Psoriasis Area and Severity Index (PASI) of 23 (6), while patients in the PsA study IMPACT 2 had a mean PASI of 11 (7); differences in other clinical development programmes are even more profound.

As these differences can, in part, be explained by the inclusion criteria of the respective trials, single-centre experiences are relevant and telling. Analysing 319 consecutive patients with PsA, Cauli et al. (8) found very low correlations between tender or swollen joint

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Table I. *Arguments in favour or against psoriasis (PsO) and psoriatic arthritis (PsA) being flip sides of the coin*

Approach	Method	Argument to "lump"	Argument to "split"	Comment
Clinical observation	Anatomical studies on DIP joints and nails	Anatomical proximity may directly link enthesitis of DIP joints to nail bed changes		DIP involvement is not always associated with nail psoriasis
	Baseline characteristics of clinical studies		Substantial differences regarding baseline PASI between PsO and PsA studies	Bias introduced by inclusion criteria
	Correlating skin and joint assessments in the same patients		No correlation between tools assessing the different domains (skin vs. joints)	Cross-sectional studies only
Genetics	Genome-wide association studies	Multiple shared genetic susceptibility loci	Few distinct genetic susceptibility loci	Bias introduced by PsO being part of both traits
	Dense sequencing		Several loci exclusively associated with PsA	
Animal models	Epidermal deletion of JunB and c-Jun	Phenotype comprises skin and joint inflammation	On a RAG2 background, the joint phenotype is not observed	Efficacy of T-cell directed anti-psoriatic therapies argues against the relative unimportance of T cells in PsO
	Collagen antibody-induced arthritis model	$CD3^+$ cells responding to IL-23 drive enthesitis in B10.RIII mice		This model does not comprise a skin phenotype
	F759 and K5.Stat3C double-transgenic mice		Distinct pathways underlie skin and joint inflammation. Skin inflammation facilitates arthritis of neighbouring joints	A "deep Koebner phenomenon" might link skin and neighbouring joint inflammation
Clinical studies	Head-to-head ustekinumab (blocking IL-12 and IL-23) vs. etanerceptin PsO		Superior efficacy of ustekinumab vs. etanercept in PsO	Etanercept is regarded the least effective TNF-α inhibitor in PsO
	Head-to-head guselkumab (blocking IL-23) vs. adalimumab in PsO		Efficacy of guselkumab at least equivalent to adalimumab	Adalimumab is regarded a more effective TNF-α inhibitor in PsO compared with etanercept
	Head-to-head anti IL-17 antibodies vs. etanercept/ ustekinumab in PsO		Superior efficacy of ixekizumab vs. etanercept and of secukinumab vs. etanercept and ustekinumab	Ustekinumab was regarded the most effective anti-psoriatic biologic prior to approval of secukinumab
	Tissue gene expression	PsA signature closer related to PsO than to other types of arthritis	Substantial differences in skin and synovial signatures	Correlates well with efficacy data of clinical studies using biologics in PsO and PsA

DIP: distal interphalangeal joint; PASI: Psoriasis Area and Severity Index; TNF-α: tumour necrosis factor alpha; IL: interleukin; RAG2: Recombination-Activating Gene 2.

counts on the one hand and the PASI on the other hand, as well as between patient assessment of skin diseases vs. joint disease. The International Psoriasis Council investigated the same question, by applying sets of assessment tools for symptoms of skin, nails and joints in 180 patients with PsO and PsA. Good correlations amongst the results obtained for activity and severity measurements of skin or joint symptoms were observed using these sets of tools, while there was again no correlation between tools assessing different domains (9).

Taken together, the courses of PsO and PsA in the same patient seem not to correlate, thus favouring the concept of them being 2 separate entities with no direct pathogenetic link.

GENETIC STUDIES

A decade of genome-wide association studies has substantially deepened our understanding of PsO. Most of these studies confirmed an early finding that a locus on chromosome 6p was associated with the risk of developing PsO. They also suggested HLA-Cw6 to be the susceptibility allele within what is now called the psoriasis susceptibility locus 1 (PSORS1). To date, PSORS1 is by far the most strongly associated locus with PsO, thought to account for approximately 50% of the heritability of the disease (10, 11). Meanwhile, approximately 40 additional loci have been found to be associated with PsO. Many of the potentially corresponding genes point towards a central role of both the innate as well as the adaptive immune system (12–14). They are involved in 4 broad immunological processes, namely skin barrier function, the NFκB pathway, T-cell signalling, and antigen presentation (15). These genetic studies were instrumental when revising the current hypothesis on PsO pathogenesis, assigning important roles, namely to TH17 lymphocytes, neutrophils, dendritic cells, and keratinocytes

as cellular key players on the one hand, and TNF-α, interleukin (IL)-23, IL-17A, and IL-22 as crucial mediators on the other hand (1, 16).

Familial aggregation, demonstrating a strong genetic component, is a feature of PsO as well as of PsA. A large genealogical study performed in Iceland calculated the recurrence risk ratio for first-degree relatives to be much higher for PsA compared with PsO, suggesting a substantial difference in the genetic architecture of the 2 diseases with a heavier genetic burden in PsA (17, 18). It comes as no surprise that the majority of genetic susceptibility loci identified to date in PsA is shared with PsO, as the latter is present in both traits; this is true for all 4 fundamental immunological processes mentioned above (15). The large degree of overlap indicates pleiotropic effects within these shared molecular pathways. A well-established example to support genetic differentiation involves the associations with genes in the human leukocyte antigen (HLA) class I region of the major histocompatibility complex on chromosome 6: while HLA-C*06 is specific for PsO, numerous HLA-B alleles confer risk specifically for PsA (19). Following up on this observation and elaborating on the genotype-phenotype correlation, Fitzpatrick's group recently published evidence pointing towards different HLA susceptibility genes being associated with particular features that defined the PsA phenotype of a given patient. Furthermore, they found that additive interactions between different susceptibility HLA alleles define the propensity for a more severe or milder musculoskeletal phenotype (20).

In an attempt to identify additional PsA-specific risk loci, a group of researchers recently published their results on dense genotyping of immune-related susceptibility loci in a collection of samples from almost 2,000 patients with PsA and approximately 9,000 healthy population controls of Caucasian ancestry (21). They reported 8 loci passing genome-wide significance. Interestingly, distinct PsA risk variants were identified at the locus of the IL-23 receptor, chromosome 5q31 was found to be a susceptibility locus specifically for PsA, and an enrichment of associated variants to markers of open chromatin in $CD8^+$ memory primary T cells was noted. The use of chromatin marks has previously been used successfully to identify relevant cell types in complex traits (22). Indeed, the particular importance of $CD8^+$ T cells in PsA pathophysiology has previously been suggested, based on numerous lines of evidence (23). Interestingly, these cells have been shown to produce IL-17 and to correlate with clinical measures of disease activity (24).

In summary, the considerable genetic overlap of PsO and PsA noted so far may be explained based on the composition of the cohorts studied. As dense genotyping progresses, substantial differences in the genetic architecture of the 2 diseases are unravelled. IL-17 and IL-23 seem to be relevant cytokines in PsO as well as in PsA; $CD8^+$ cells might be particularly important in the pathophysiology of PsA.

ANIMAL MODELS

Multiple animal models have been established to foster different aspects of research in PsO, several of which are regularly used to study the pathophysiology of PsO or for the purpose of drug discovery (25). In the field of PsA, there is a lively discussion to which extent the models used faithfully mirror the human disease (26). For the purpose of this review, it is particularly important to discuss models exhibiting a phenotype comprising skin and joint changes.

In 2005, Zenz et al. (27) reported that epidermal deletion of *JunB*, a component of the AP-1 transcription factor localized in the *PSORS6* on chromosome 19p13, and its functional companion *c-Jun* in adult mice leads to a phenotype resembling the histological and molecular hallmarks of PsO as well as PsA. When similar deletions were introduced in recombination-activating Gene 2-deficient mice, the skin phenotype was still preserved, although less pronounced, suggesting a minor role for lymphocytes in their pathogenesis. In contrast, joint symptoms were basically absent, pointing towards a key role of lymphocytes with regard to this part of the phenotype. Finally, the same deletions in TNF receptor 1 (TNFR1) deficient mice could not prevent onset of the skin phenotype, but joint inflammation was almost completely abrogated, pointing towards a more important role of TNF-α in PsA compared with PsO. According to this experimental approach, PsO would depend less on T cells and TNF-α than would PsA.

Sherlock et al. (28) used the collagen antibody-induced arthritis (CAIA) model to study the role of T cells and IL-23 in PsA. In this model, injection of type-II-collagen-specific antibodies induces broad articular inflammation and synovitis; in B10.RIII mice enthesitis is a prominent feature. The authors show that IL-23 promotes highly specific entheseal inflammation by acting on $CD3^+$ entheseal resident lymphocytes. These cells allow enthuses to respond to IL-23 in the absence of further cellular recruitment and to elaborate inflammatory mediators including IL-6, IL-17, IL-22 and chemokine (C-X-C motif) ligand 1 (CXCL1). The expression of IL-23 was found to be sufficient to phenocopy the human disease, with the specific and characteristic development of enthesitis and entheseal new bone formation.

While induction of nail psoriasis is thought to be in part due to enthesitis of distal interphalangeal joints (see above), a recent report provides evidence for a "skin-bone-axis", with cutaneous inflammation facilitating the onset of arthritis in a mouse model (29): the authors crossed F759 mice spontaneously developing autoimmune arthritis after one year of age with

K5.Stat3C transgenic mice, the latter exhibiting PsO-like skin changes due to constitutively active Stat3C in keratinocytes. F759 mice harbouring the K5.Stat3C transgene not only had aggravated skin lesions, but also spontaneously developed arthritis with high penetrance in adjacent paws as early as 3 weeks of age. Furthermore, enforced generation of PsO-like lesions in F759 mice by topical application with 12-O-tetradecanoylphorbol-13-acetate (TPA) induced swelling of the underlying joints. In summary, the authors suggest that the transition from PsO to PsA occurs through the cross talk of non-immune cells and epidermal and entheseal cells via IL-6 and the IL-23/Th17-associated Stat3 activation. Extrapolation of the situation in man is difficult: while elbows and knees are the classic predilection sites for PsO, PsA of the respective joints is relatively rare. However, the concept of skin proximity and a potential "deep Koebner phenomenon" is more pertinent for hands and feet, where PsA manifestation is more common.

It can be concluded that animal models exist that comprise key features of PsO as well as PsA. In these models, both diseases can readily be separated from each other, as distinct pathomechanisms contribute to each of them. Interestingly, there is some evidence that PsO-like skin inflammation might trigger arthritis in neighbouring joints.

CLINICAL STUDIES

There is a huge body of literature on the efficacy of systemic anti-psoriatic therapies in PsA and vice versa, many of them show efficacy in both indications (30, 31). Despite a recent study on methotrexate in PsA not meeting its primary end point (32), many experts still consider this drug to be an eligible therapeutic option in PsA as well. However, not all drugs are similarly effective in both indications. Differences observed in this regard may reflect relevant differences at the pathogenetic level; this is particularly telling when looking at drugs with well-defined modes of actions, such as biologics.

The most widely used biologics to treat PsO or PsA to date are TNF-α inhibitors. All biologics with this mode of action exhibit robust and comparable efficacy in PsA when using the American College of Rheumatology (ACR) response criteria. They are equally well established to treat PsO, although the different drugs exhibit distinct profiles with regard to mode of onset and efficacy in this indication (33).

Using TNF-α inhibitors as a benchmark, ustekinumab, blocking both IL-12 as well as IL-23 through binding to the common p40 subunit, showed superior efficacy in a head-to-head trial vs. etanercept in PsO (34). Although direct comparator studies are not available in PsA, most experts consider ustekinumab to be inferior to TNF-α inhibitors in PsA, a notion supported by the results of placebo-controlled phase III studies in that indication (35). Biologics specifically inhibiting IL-23 through binding to its p19 subunit are in clinical development, and preliminary evidence suggests that one of them, guselkumab, might be at least as effective as, or even superior to the TNF-α inhibitor adalimumab in the treatment of PsO (36). Finally, several IL-17 inhibiting biologics are either already approved or far advanced in their clinical development programme. Two of them, secukinumab and ixekizumab, have shown superior efficacy in the treatment of PsO compared with etanercept (37, 38), the former also in comparison to ustekinumab (39). Numerically, response rates of these drugs seem comparable to those of TNF-α inhibitors in PsA, although direct comparator studies are lacking (40, 41).

Overall, these observations suggest that TNF-α is a key cytokine in PsO and PsA alike, while IL-17 may be particularly important in the context of PsO. Experts interpret the phase III trial data of secukinumab and ixekizumab in PsA to be comparable to those of TNF-α inhibitors (A. Kavanaugh & C. Ritchlin, personal communication, Division of Rheumatology, Allergy and Immunology, University of California San Diego, USA, and Division of Allergy Immunology and Rheumatology, University of Rochester, USA), while their efficacy in PsO sparked a discussion on whether or not the current treatment goal, namely a reduction in the so-called PASI by 75% should be replaced by a more ambitious one, such as a response of 90% or more (42). This notion is supported by a recent gene expression study, documenting distinct gene expression patterns in skin vs. synovium of PsA patients. In this study, the PsA gene expression profile is more closely related to that of PsO than to other types of arthritis. But there were still substantial differences, as skin showed a stronger IL-17 gene signature than PsA synovium, while TNF-α and interferon gamma gene signatures were more equivalent in both tissues (43).

CONCLUSIONS AND PERSPECTIVES

Considering the evidence, a picture emerges indicating a set of key components driving PsO and PsA. These comprise T cells, TNF-α, IL-17, and IL-23. To this end, this would support the idea of PsO and PsA representing flip sides of the coin. However, the above-mentioned components do not constitute the whole picture, and substantial differences exist when analysing the importance of each of these in the context of both pathologies, and with regard to T cells also the relevant subpopulations. In recent years, the most compelling evidence for PsO and PsA representing distinct entities comes from genetic studies, as namely dense genotyping helps to split what was lumped together previously.

Physicians can still rely on PsO as the most valuable biomarker for the potential presence of PsA, helping

Table II. *Practical consequences from regarding psoriasis (PsO) and psoriatic arthritis (PsA) as distinct entities*

Conclusion	Practical consequence
Disease activities of PsO and PsA do not correlate.	Any PsO patient needs to be screened for presence of PsA
Genetics and pathogenesis of PsO and PsA overlap: • TNF-α is important in PsO as well as PsA • IL-17 is particularly important in PsO	TNF-α inhibition remains (so far) the gold standard for treating PsA, while IL-17 inhibition exhibits the highest efficacy in the treatment of PsO observed so far
Genetics and pathogenesis of PsO and PsA differ: • Separate susceptibility loci for PsO and PsA	To develop novel drugs effective in PsO as well as PsO, targeting ”common check points” in signal transduction cascades rather than ”common denominator” cytokines or cells may be a successful strategy

TNF-α: tumour necrosis factor alpha; IL: interleukin.

them to achieve a major objective in the management of these patients, namely early identification and implementation of an effective therapy, as a delay of more than 6 months is associated with inferior long-term outcome of therapy (44, 45) (Table II).

Scientists will undoubtedly dig deeper into the differences between PsO and PsA to better understand their respective pathophysiologies. At the same time, identifying novel targets to treat PsO as well as PsA remains an important objective in drug discovery, as drugs with convincing efficacy in both entities would make treatment regimens simpler and thus patient-friendlier (46) (Table II). These targets will most likely represent “common check points” of inflammation, for example in signal transduction cascades, rather than “common denominators” such as cytokines. Examples of this approach are small molecules inhibiting enzymes such as janus kinases or phosphodiesterase 4, both approaches have proven to be effective in PsO as well as in PsA (47, 48).

Conflicts of interest. W-HB has received honoraria as a speaker or advisor from the following companies: Abbvie, Amgen, Biogen Idec, Celgene, Covagen, Janssen, Leo, Lilly, MSD, Novartis, Pantec Biosolutions, Pfizer, and UCB.

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