Excerpta from Volume 96 of ActaDV

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In an attempt to illustrate the width and novelty of clinical and experimental research presented in Acta Dermato Venereologica, the Editor-in-Chief Anders Vahlquist has selected 20 out of nearly 250 publications in 2016. Here, a short commentary on each of the papers from 5 different research areas is presented (in alphabetical order).

Cancer

The first paper in volume 96 of ActaDV is a review by Professor Irene Leigh and her co-workers in London and Dundee (1), describing the promise of genomics in dissecting various disease mechanisms in squamous cell carcinoma (SCC), with the ultimate goal of finding new treatment targets (Fig. 1). Among the many possible therapies, inhibitors of various epidermal growth factors and immunomodulatory drugs are discussed in some depth.

In another report, Professor Nicole Basset-Seguin and her team in Paris present the results of photodynamic therapy (PDT) in 105 cases of Bowen's disease, focusing on the relapse rates of invasive cancers (2). SCC occurred post-PDT in 16 out of the treated fields, but whether or not these "treatment failures" originated from microscopic nests of pre-existing SCC within the Bowenoid lesions before PDT is not known. However, the results remind us about the importance of careful follow-ups of PDT-treated Bowen's disease, especially in immunosuppressed individuals.

Immunosuppression is also a factor of importance in the context of basal cell carcinoma (BCC). In a Danish study, Omland et al. examine the role of regulatory T cells (T-regs)

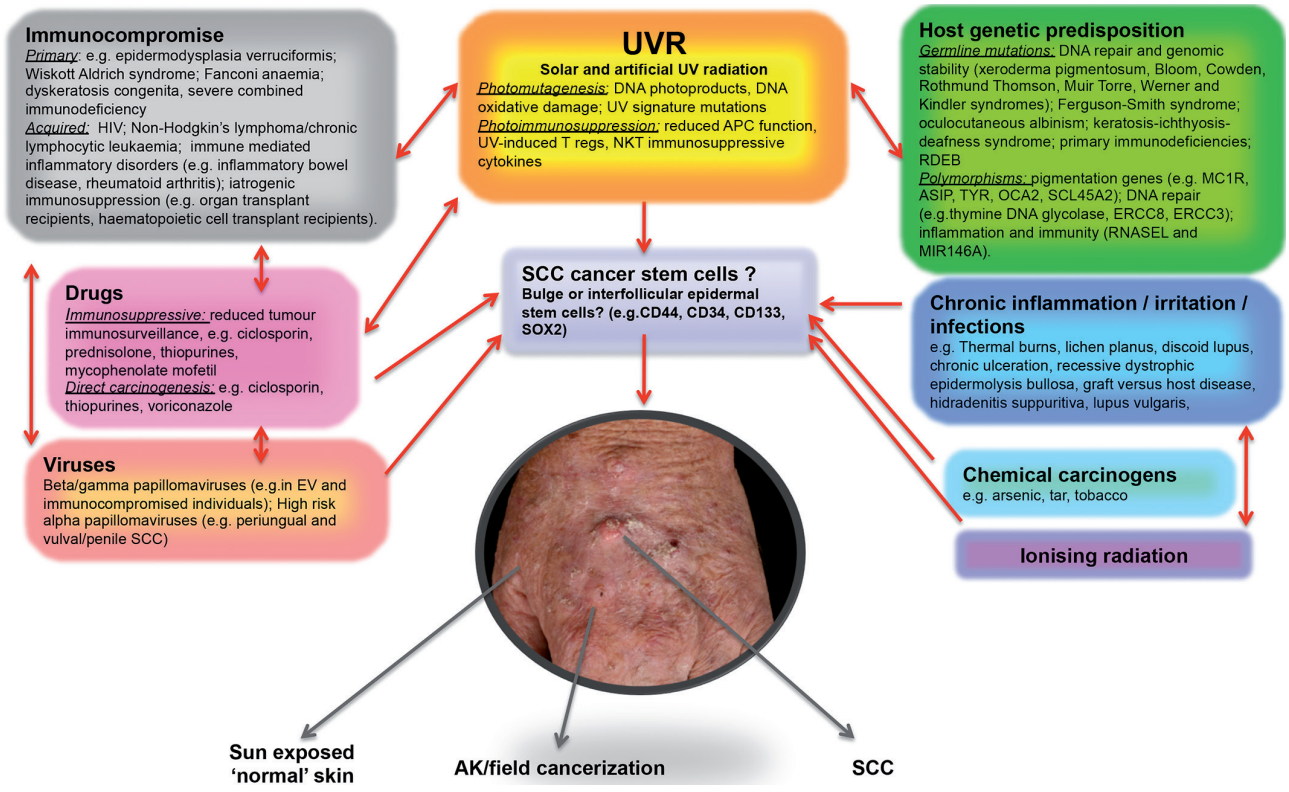


Fig. 1. Summary of aetiology factors in cutaneous squamous cell carcinoma (SCC). AK: actinic keratosis. (From ref 1 with permission from Acta Derm Venereol).

in the environment of BCC (3). T-regs suppress conventional T cells maintaining immunological tolerance. The impact of T-regs on skin malignancy is already well documented in malignant melanoma and SCC, but their role in BCC is poorly understood. This study compared T-reg density of facial BCC within peritumoural skin and non-UV-exposed skin. The results provide preliminary evidence for the existence of an immunosuppressed niche in facial skin surrounding BCCs, which may have consequences for the malignant development.

Immunological factors affecting skin cancer are also discussed by Trapp et al. (4), although this time in relation to various stress coping strategies in patients with melanoma. In an exploratory case control study, the Austrian group investigated the lymphocyte subpopulations and stress coping strategies in 18 non-metastatic melanoma patients and 18 controls with benign skin diseases. In melanoma patients significant positive correlations between certain lymphocyte populations (positive for CD3, CD4, CD19 and CD45) were found with regards to coping strategies characterized by diversion of stress and focusing on stress-compensating situations. In the authors´ view, this field of research deserves further multi-professional investigations in order to provide new therapeutic approaches in the treatment and understanding of melanoma patients.

The efficacy of various topical treatment options for actinic keratosis (AK) are evaluated in a systematic review by Stockfleth, Sibbring and Alarcon from Germany, UK and Spain (5). They focus on 0.5% 5-fluorouracil in 10% salicylic acid (5-FU/SA), ingenol mebutate (IMB) and imiquimod 2.5%/3.75% (IMI). Eleven publications, relating to 7 randomized controlled studies met the inclusion criteria. Complete clinical clearance was higher for 5-FU/SA (55%) than for IMB (43%) and IMI (25/31%), and the former drug was also associated with less recurrences. However to corroborate these findings, the authors call for new, long-term trials with comparable outcome measures.

Psoriasis

In a review article by Professor Wolf-Henning Boehncke, Geneva (6) the relationship between psoriasis (PsO) and psoriatic arthritis (PsA) is discussed under the title: Flip Sides of the Coin? The issue of whether PsO and PsA are distinct entities, or part of the spectrum of a "psoriatic disease" is again ventilated, this time based on new results from genetic studies, animal models and clinical research. The strongest arguments for PsO and PsA being distinct entities come from recent genetic studies, so called dense genotyping, and by the fact that the disease activities in PsO and PsA do not seem to correlate. Arguments favouring the idea of PsO and PsA being variants of the same disease are that key immunological components driving PsO and PsA appear to be the same, and that most systemic treatments for psoriasis work equally well in both diseases. However the final answer to "Flip sides of the coin?" is still in the air and will probably remain so forever.

A long suspected PsO-aggravating factor is streptococcal throat infections. In a study by Thorleifsdottir et al. (7), 275 psoriasis patients were examined and 72% of those with confirmed streptococcal infection reported aggravation of psoriasis. Notably, women and patients with early onset psoriasis were more likely to report aggravation, and 49% of patients reported improvement after tonsillectomi.

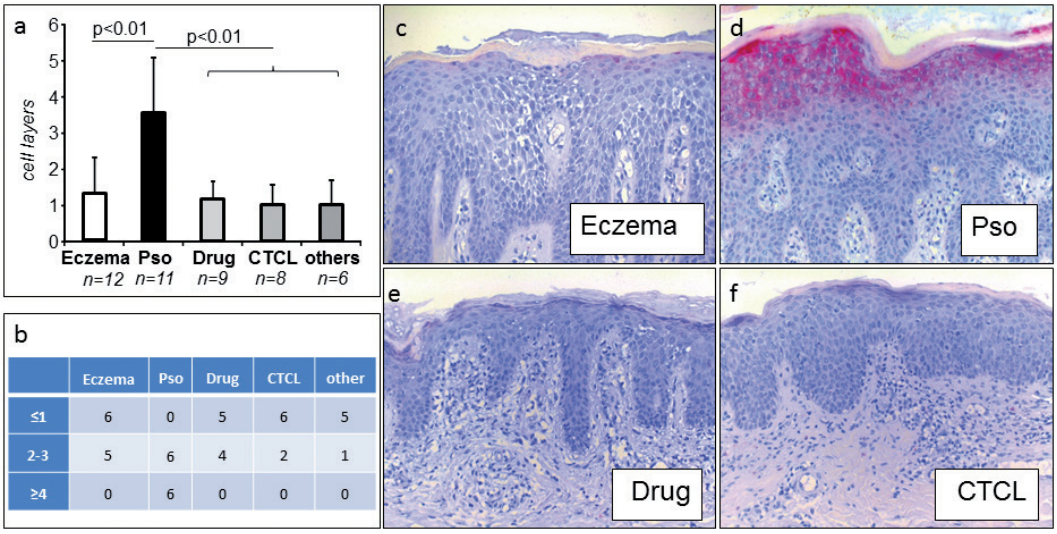
Another precipitation factor in psoriasis is the interplay between itch and psyche, also involving Köbnerisation due to scratching. In an update on this topic, Reich et al. (8) discuss the complex interaction between depression, poor psychosocial well-being, itch and psoriasis, together creating a vicious circle of aggravating factors.

Fortunately there are now many effective drugs available for psoriasis. In a systematic review, Zweegers et al. (9) compare the effectiveness of biological and conventional systemic therapies in daily practice in adults with plaque psoriasis. The literature was searched for trials on adalimumab, eternacept, infliximab and ustekinumab, acitretin, cyclosporine, fumarates and methotrexate. Although large ranges were noted in the percentage of patients reaching PASI75, especially for the 2 first drugs, the results were generally quite good. Combination therapy of biologics with conventional systemic agents, and dose adjustment of biologics were frequent strategies to enhance the treatment response, which may explain the large range in improvement between cohorts.

Needless-to-say, making a correct diagnosis of psoriasis is a *sine qua non* for prescribing optimal treatment, but is not always so easy to accomplish. Erythroderma is one example of a difficult-to-diagnose condition that can be caused by psoriasis, eczema, T-cell lymphoma, drug reactions, as well as several other rare diseases. It is of interest therefore that Braegelmann et al. (10) have now identified interleukin-36 (IL-1F9) as a good immunohistochemical marker for psoriasis erythroderma, thus helping to exclude other causes (Fig. 2).

Psychodermatology

As already exemplified above, an increasing number of studies concerning psychological aspects of skin and venereal disease is now published in ActaDV, being the official journal of the European Society for Dermatology and Psychiatry (ESDaP). This collaboration is further highlighted by supplement 217, "Frontiers in Psychocutaneous Diseases: Selected Writings in Psychosomatics, Psycho-dermatology and Psycho-neuro-endocrine-immunology" (Fig. 3), dedicated to the memory of Professor Emiliano Panconesi, the first President of ESDaP and



	Eczema	Pso	Drug	CTCL	other
≤1	6	0	5	6	5
2-3	5	6	4	2	1
≥4	0	6	0	0	0

Fig. 2. Interleukin (IL)36γ expression in different erythroderma subsets. (a) Number of IL-36γ-positive cell layers detected by immunohistochemistry in the different disease subsets (mean expression ± standard error of the mean (SEM)). (b) Number of specimens with low (0–1 cell layers), fair (2–3 cell layers) and strong (≥ 4 cell layers) expression of IL-36γ within the different subsets. (c–f) Representative IL-36γ-micrographs (eczema, psoriasis (Pso), drug-reaction and cutaneous T-cell lymphoma (CTCL), original magnification × 200, respectively). (From ref 10 with permission from Acta Derm Venereol).

one of the founding members of EADV. A few titles from this supplement illustrate its almost textbook-like content: "From evidence-based medicine to human-based medicine in psychosomatics" (11), "Psychodermatology in clinical practice" (12), and "Delusional infestations: State of the Art" (13).

Various psychological aspects of psoriasis, including the efficacy of biofeedback and cognitive-behavioural therapy, are also covered in this supplement, as well as in some original reports in the regular issues of ActaDV. One example is a recent Danish study about the association between psoriasis and new-onset depression (14). One important finding in this study is that severe psoriasis especially in younger individuals may itself be a risk factor for new-onset depression.

Fig. 3. Front cover of Supplement 217, 2016.

Rosacea

In a review article by Professor Bodo Melnik, Germany (15), novel aspects about the pathogenesis of rosacea are covered; a major conclusion is that the Celtic genetic heritage in the European population might be blessed for increasing our life expectance, but at the same time can be blamed for the high incidence rosacea, especially in the Nordic countries. The Janus-like effects of cathelicidin antimicrobial peptide (CAMP) are highlighted; on the one hand protecting against mycobacteria and on the other hand causing a readiness to intense skin inflammation. The theory goes like this: The expression of CAMP is upregulated by vitamin D-dependent (VDR) and independent (C/EBP) transcription factors, the former of which will be insufficient during UV-deficient conditions (Fig. 4). Celts however appear evolutionary to have overcome the geographical disadvantage of deficient CAMP production during wintertime via activation of the alternative, C/EBP pathway, thus retaining a good protection against mycobacteria. However, C/EBP is also a transcription factor of Toll-like receptor (TLR)-mediated innate immune reactions and cellular stress responses, which may explain the reduced threshold for skin stressor in patients with rosacea and a Celtic ancestry.

These ideas about rosacea pathogenesis, also presented in many other journals, will no doubt initiate a search for new

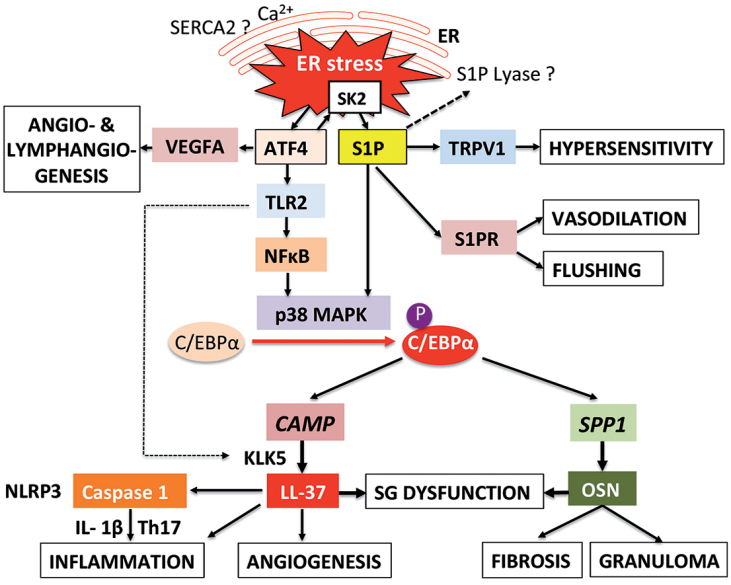


Fig. 4. Endoplasmic reticulum (ER) stress-centred working model of rosacea pathogenesis. Upregulated ER stress via transcription factor 4 (ATF4) and S1P activates p38 mitogen-activated protein kinase (p38 MAPK) that phosphorylates and activates CCAAT/enhancer-binding protein-α (C/EBPα). C/EBPα increases the expression of cutaneous antimicrobial peptides (CAMP) and osteopontin (OSN) stimulating inflammation, angiogenesis, fibrosis and granuloma formation. S1P induces skin hypersensitivity and causes vasodilation and flushing. Toll-like receptor 2 (TLR2) increases the activity of kallikrein 5 (KLK5) enhancing the proteolytic cleavage of *CAMP*. Upregulation of TLR2 on peripheral neurones increases the susceptibility for pain. Bioactive peptide of CAMP (LL-37) activates caspase-1, the key enzyme of the NLRP3 inflammasome producing interleukin-1β (IL-1β), which activates Th17 cells. (Text modified from ref 15; with permission from Acta Derm Venereol).

therapies which inhibit the stress mediators and down-regulate TLR in the skin. Another example of the current focus on skin inflammation is the paper by Steinhoff et al (16), reviewing the pathoaetiology and treatment options in facial erythema of rosacea.

Sexually transmitted infections

Syphilis, once the biggest simulator in Medicine, is becoming increasingly common again but is still occasionally difficult to diagnose and treat, especially in immunosuppressed patients. In a study from Copenhagen, Salado-Rasmussen et al. (17) investigate the serological response to treatment with doxycycline compared with penicillin in 202 HIV-infected individuals. They conclude that doxycycline is a favourable option in this group of patients.

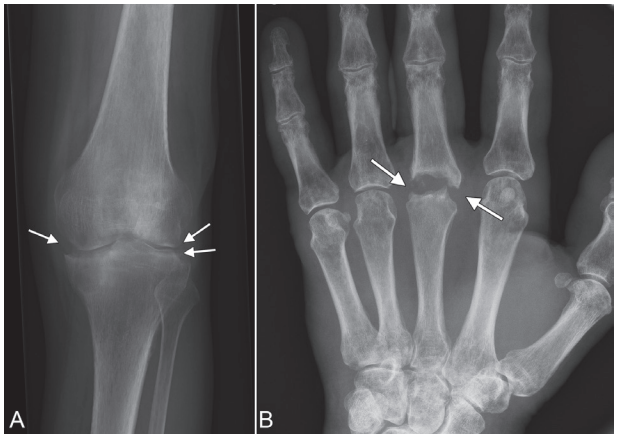


Fig. 5. (A) X-ray of the left knee joint showing reduction in height of the cartilage laterally and medially (*arrows*), fissures on the tibial articulate surface and general osteopaenia. (B) X-ray of the left hand showing that adjacent edges of the articulate surfaces in the 3rd metacarpophalangeal joint (*arrows*) are irregular and sclerotic, corresponding to status post-septic arthritis. (From ref 18 with permission from Acta Derm Venereol).

Another rare occurrence which should not be forgotten is disseminated goncococcal infection, typically presenting with fever, pustular skin lesions and joint involvement, and usually responding quickly to antibiotics. However, in a report from Gothenburg, Rehnström et al. (18) describe two cases of gonococcal osteomyelitis resulting in permanent sequelae because of a delayed diagnosis and treatment (Fig. 5).

Lastly some comforting news about STI and concurrent treatment with biologicals. There has been suspicion that anogenital HPV infections might be enhanced by treatment with immunosuppressive drugs, including TNF-α inhibitors. If so this would be of special concern in psoriasis patients who have a higher incidence of anogenital HPV infections than, for example, patients with inflammatory bowel disease (IBD), who are also candidates for biologics. However, a study of Handisurya et al. from Austria (19) now shows in 222 patients with psoriasis or IBD that there is no increased prevalence of anogenital HPV during treatment with TNF-inhibitors.

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