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Ancient friends, revisited

New aspects on the important role of nuclear receptor signalling for skin physiology and for the treatment of skin diseases

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Many members of the nuclear receptor (NR) superfamily are strongly expressed in human skin, making them a highly interesting target of dermato-endocrine research. Consequently, an increasing number of natural and synthetic NR ligands are now successfully used for the treatment of various common and rare skin disorders, including psoriasis. Moreover, the increasing awareness in the scientific community about the importance of nuclear receptor signaling for dermatology and other medical disciplines is also impressingly reflected by steadily increasing citations in PUBMED (n = 36 in 1980, n = 48 in 1990, n = 377 in 2000, n = 689 in 2010; for the term "nuclear receptor"). The articles published in this issue of *Dermato-Endocrinology*, all written by highly respected experts in their field, highlight the importance of nuclear receptor signaling for skin physiology, for the treatment of skin diseases, and for other medical disciplines.

In the first paper, Väisänen et al.[1] discuss the impact of the dynamic nature of chromatin organization, i.e. the spatio-temporal changes of chromatin region of NR target genes. They state that this dynamics is triggered by environmental changes, of which for NRs the exposure with their ligands is most critical.[1] They conclude that for an understanding of skin disorders, which involve the actions of NRs, the parameter time should be carefully considered in context of other factors that may influence the chromatin organization, and by this the responsiveness, of key NR target genes.[1]

In the second paper, Sertznig and Reichrath[2] review the role of peroxisome proliferator-activated receptors (PPARs) for skin physiology and for the treatment of skin diseases. They explain that peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors involved in the genetic regulation of lipid metabolism and energy homoeostasis, and that accumulating evidence now suggests additional roles of PPARs in genomic pathways including the regulation of cell growth, apoptosis and differentiation.[2] In their review, the authors summarize the current knowledge of PPAR functions in various skin disorders particularly those involving inflammation and epidermal hyperproliferation (i.e. psoriasis, atopic dermatitis, acne, scleroderma, skin malignancies).[2]

In the following paper,[3] Hans Törmä reviews the regulation of keratin expression by retinoids. He outlines that vitamin A and its natural and synthetic metabolites (retinoids) affect growth and differentiation of human skin, and that among the genes affected by retinoids in epidermis are keratin genes.[3] He explains that keratins are intermediate filament proteins that have essential functions in maintaining the structural integrity of epidermis and its appendages.[3] Their expressions are under strict control to produce keratins that are optimally adapted to their environment.[3] In his fascinating article, Hans Törmä reviews retinoid regulation of keratin expression in cultured human epidermal keratinocytes and in human skin in vivo.[3] He discusses the direct and indirect mechanisms involved and the novel therapeutic strategies that are proposed for utilizing retinoids in skin disorders due to keratin mutations (e.g. epidermolysis bullosa simplex and epidermolytic ichthyosis).[3]

In the fourth paper of this issue, Bodo Melnik presents a very interesting scientific hypothesis involving isotretinoin and FoxO14. He explains that oral isotretinoin (13-cis retinoic acid) is the most effective drug in the treatment of acne, restoring all major pathogenetic factors of acne vulgaris, and that isotretinoin is regarded as a prodrug which after isomerization to all-trans-retinoic acid (ATRA) induces apoptosis in cells cultured from human sebaceous glands, meibomian glands, in B16F-10 melanoma cells, neuronal crest cells and others.[4] By means of translational research, he provides in his paper[4] substantial indirect evidence for isotretinoin's mode of action by upregulation of forkhead box class O (FoxO) transcription factors. He outlines that FoxOs play a pivotal role in the regulation of androgen receptor transactivation, insulin/insulin like growth factor-1 (IGF-1)-signaling, peroxisome proliferator-activated receptor-γ (PPARγ)- and liver X receptor-α (LXRα)-mediated lipogenesis, β-catenin signaling, cell proliferation, apoptosis, reactive oxygene homeostasis, innate and acquired immunity, stem cell homeostasis, as well as anti-cancer effects.[4] He further convincingly reports that an accumulating body of evidence now suggests that the therapeutic, adverse, teratogenic and chemopreventive effecs of isotretinoin are all mediated by upregulation of FoxO-mediated gene transcription.[4] These FoxO-driven transcriptional changes

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of the second response of retinoic acid receptor (RAR)-mediated signaling counterbalance gene expression of acne due to increased growth factor signaling with downregulated nuclear FoxO proteins.[4] In his fascinating paper, Bodo Melnik convincingly discusses that the proposed isotretinoin→ATRA→RAR→FoxO interaction offers intriguing new insights into the mode of isotretinoin action and explains most therapeutic, adverse and teratogenic effects of isotretinoin in the treatment of acne by a common mode of FoxO-mediated transcriptional regulation.[4]

In the fifth paper, Paloma Pérez reviews the role of glucocorticoid receptors (GR) for epidermal homeostasis and hair follicle differentiation.[5] She explains that glucocorticoids (GCs) exert their biological and therapeutical actions through the GR, a ligand-dependent transcription factor, and that synthetic GC derivatives are widely prescribed for treating numerous cutaneous inflammatory and immune diseases due to their great efficacy.[5] However, it is well known that chronic treatment with GCs produces adverse side-effects including skin atrophy, delayed wound healing and in certain cases GC resistance.[5] She outlines that while the mechanisms underlying the therapeutic actions of the GR in skin have been extensively studied; in contrast, the role of GR as a modulator of epidermal development and homeostasis has received less attention.[5] She explains that the ubiquitous functional inactivation of GR results in defective epidermal formation although the underlying mechanisms have not been fully characterized.[5] She reports that the use of transcriptomic approaches both in vitro and in vivo allowed the identification of genes that are regulated by GR in developing and adult skin.[5] She outlines that a main goal to understand the role of GR in skin biology is to identify primary transcriptional targets as well as the signaling pathways mediating GR action.[5] Furthermore, it is important to decipher the contribution of GR in the different cellular compartments of the skin, including keratinocytes of the interfollicular epidermis and hair follicles, and their respective stem cell progenitors.[5] She explains that recent findings indicating that the skin acts as a true peripheral endocrine organ imply greater complexity than originally thought,[5] and that the local production of GCs and other steroid hormones should be considered as a modulator of skin function under homeostatic and diseased conditions.[5] Finally, studying GR function in skin should take into account that the mineralocorticoid receptor may also mediate GC actions and/or regulate transcription either by itself or in combination with GR.[5] She concludes that addressing all these issues should help to elucidate the mechanisms by which GR contributes to establishment of a competent epidermal barrier and may also have implications in the context of dermatological treatments based on GC-analogs.[5]

In the following paper of this issue, Schoepe et al. review the use of test systems for the determination of glucocorticoid receptor ligand induced skin atrophy.[6] They report that topical glucocorticoids are highly anti-inflammatory effective but limited by their side effect potential, with skin atrophy being the most prominent one.[6] They explain that determining the atrophogenic potential of novel compounds targeting the glucocorticoid receptor is important and that significant progress in the understanding of glucocorticoid receptor mediated molecular action has been made providing the basis for novel glucocorticoid receptor ligands with a potentially superior effect/side effect profile.[6] Such new compounds, however, have to be tested. Schoepe et al. outline that the present gold standard for the reliable prediction of glucocorticoid induced skin atrophy are still in vivo models, however, in vitro models may replace them to some extent in the future.[6] They report that indeed, advances in technologies to determine the atrophogenic potential of compounds in vitro has been made recently and promising novel test models like the human full thickness skin models are emerging.[6] Their full predictive value, however, needs to be further evaluated.[6] The authors convincingly conclude that currently, a screening approach starting with a combination of several in vitro test systems followed by subsequent testing of the most promising compounds in rodent models is recommended prior entering clinical studies with selected development compounds.[6]

The following papers[7-11] highlight the importance of the cutaneous vitamin D endocrine system (VDES) for skin physiology, for skin carcinogenesis, for the treatment of skin diseases, and for various other disorders. In the seventh paper of this issue, Trémezaygues and Reichrath give an overview on the use of calcitriol and analogs in the treatment of psoriasis.[7] They explain that vitamin D and analogs exert in the skin and other tissues potent effects on cellular differentiation and proliferation.[7] Moreover, these compounds regulate apoptosis and exert immunomodulatory effects in many cell types.[7] The authors report that, during the last decades, it has convincingly been shown that vitamin D compounds are effective and safe in the topical treatment of psoriasis, where they nowadays represent a standard therapy.[7] In their review, Trémezaygues and Reichrath summarize laboratory and clinical investigations related to the treatment of psoriasis with calcitriol or analogs.[7] Additionally, they discuss promising concepts for the development of new vitamin D analogs.[7] As a matter of fact, the final goal to create strong antiproliferative or antiinflammatory acting vitamin D analogs that exert only minor calcemic activity has not been reached yet.[7] The authors conclude that new agents that may activate selective vitamin D signalling pathways but may exert only negligible calcemic activity would declare a new era in dermatologic therapy and may also be effective in the topical or systemic treatment of various inflammatory skin diseases including atopic dermatitis, and in various cutaneous malignancies, including lymphomas, squamous cell carcinoma or basal cell carcinoma.[7]

In the following paper, Hekla Sigmundsdottir reports on new aspects on immunoregulation by vitamin D analogs.[8] She outlines that the skin is a vital organ that plays a crucial role in defending us from pathogens, involving multiple players from the innate and adaptive immune system, such as neutrophils, dendritic cells, lymphocytes and antimicrobial peptides.[8] Chronic inflammatory skin diseases can be mediated by inflammatory T cells and their interactions with other cells in the skin.[8] Vitamin D is generated in the skin upon sun exposure and has a variety of effects.[8] Calcitriol and its analogs are used with success in treating mild to moderate T cell-mediated skin diseases including psoriasis, but how they mediate the beneficial effects is not well understood.[8] In the recent years, emerging evidence is rising that

modulation of the immune system by vitamin D analogs plays a major role.[8] It has been shown that vitamin D analogs can induce the generation of regulatory T cells, which are able to suppress proliferation and alter the function of inflammatory T cells.[8] Hekla Sigmundsdottir concludes that this may help explain the therapeutic effects that are observed and at the same time give hope that in combination with other therapy or used alone, vitamin D analogs may be helpful when treating more severe forms of the diseases.[8]

In the following very interesting paper, Bill Grant reviews the role of solar ultraviolet-B irradiance and vitamin D in reducing risk of dental caries.[9] He explains that large geographical variations in dental health and tooth loss among US adolescents and young adults have been reported since the mid-1800s,[9] and that studies in the 1920s and 1930s noted that vitamin D and ultraviolet-B (UVB) irradiance reduced caries formation, the proposed mechanism being improved calcium absorption and metabolism.[9] In his paper, Grant reviews the history of studies of dental caries with respect to vitamin D, geographical location and available solar UVB doses.[9] In addition, data on mean dental health rank by state for US servicemen from three periods, 1918, 1934 and 1943, were used in regression analyses with respect to summertime solar UVB doses and an index for mottled enamel, a proxy for natural fluoridation of drinking water, for 1935.[9] The author demonstrated a significant inverse correlation for dental health rank with respect to solar UVB from doses of 4.0 to 6.5 kJ/m^2 with little change thereafter.[9] Adding data for mottled enamel rates for the states with UVB doses <6.6 kJ/m^2 improved the adjusted R^2 from 0.45 to 0.52.[9] The author concluded that the mechanism whereby UVB reduces risk of dental caries is likely through production of vitamin D, followed by induction of cathelicidin and defensins, which have antimicrobial properties.[9] Additionally, he concluded that serum 25-hydroxyvitamin D concentrations at or above 30–40 ng/ml should significantly reduce the formation of dental caries,[9] and that it is unfortunate that the UVB and vitamin D findings were not given more consideration in the 1950s as a way to reduce the risk of dental caries when water fluoridation was being proposed.[9] It can be speculated that Grant's findings reported in this article may have a tremendous impact on dental health.

In his second paper published in this issue, Bill Grant discusses another very important topic: the effect of interval between serum draw and follow-up period on relative risk of cancer incidence with respect to 25-hydroxyvitamin D level.[10] He also discusses implications for meta-analyses and setting vitamin D guidelines.[10] He outlines that ecological studies have reported strong inverse correlations between indices of solar ultraviolet-B (UVB) doses and incidence and/or mortality rates for many types of cancer,[10] and that case-control studies (CCS) generally find inverse correlations between serum 25-hydroxyvitamin D [25(OH)D] concentration measured at time of diagnosis for cancer incidence, whereas nested case-control studies (NCCS), which involve a several-year follow-up time after serum sampling, generally do not.[10] In his paper, Grant examines the relation between follow-up interval and relative risk (RR) for breast, colorectal and prostate cancer.[10] He plotted the RR versus serum 25(OH)D data as a function of follow-up time from the literature for each type of cancer.[10] For breast cancer, RRs were significantly reduced only for follow-up periods less than three years. For colorectal cancer, RRs were generally significantly reduced for follow-up periods up to 12 years. For prostate cancer, RRs were not statistically significant from 4 years to 28 years. This study included no CCS. He concluded that follow-up periods after serum sampling should not be too long for breast cancer because once a tumor reaches a diameter of 1–3 mm, it requires angiogenesis to continue growing, and vitamin D reduces angiogenesis around tumors.[10] Moreover, Grant reports that breast cancer diagnoses are more common in spring and fall than in summer or winter, indicating that they can grow rapidly if circulating 25(OH)D drops in the fall or melatonin levels drop in spring.[10] Serum sampling should be conducted during the study, perhaps every two years, to overcome the problem of change of 25(OH)D concentration during cohort studies.[10]

In the following paper of this issue of *Dermato-Endocrinology*, Denzer et al. review the impact of vitamin D receptor (VDR) polymorphisms on skin cancer.[11] They explain that skin cancer is the most common cancer in humans and that the associations of VDR polymorphisms with skin cancer risk are not well characterized so far.[11] To make the most of the available information on VDR polymorphisms and skin cancer, the authors undertook a systematic review of published studies.[11] They conclude that the data summarized in this review support the concept that the vitamin D endocrine system (VDES) is of importance for pathogenesis and progression of various types of skin cancer.[11]

Last but not least, JD Safer discusses thyroid hormone action on skin.[12] He reports that the skin characteristics associated with thyroid hormone are classic, and that the name "myxedema" refers to the associated skin condition caused by increased glycosaminoglycan deposition in the skin.[12] He explains that generalized myxedema is still the classic cutaneous sign of hypothyroidism, being caused by deposition of dermal acid mucopolysaccharides, notably hyaluronic acid.[12]

In summary, the articles published in this issue report and discuss various new aspects on the important role of members of the nuclear receptor (NR) superfamily and their corresponding ligands for skin physiology and for the treatment of skin diseases. Moreover, this issue includes significant contributions to the rapidly growing fields of translational research and nutrigenomics. To put it in a nutshell, the articles published in this issue highlight the importance of nuclear receptor signalling, and of *Dermato-Endocrinology*, not only for a broad variety of common or rare skin diseases, but also for internal medicine and other medical disciplines.

References

1. Väisänen S, Matilainen J, Carlberg C. Dynamic nature of transcriptional regulation of nuclear receptor target genes in the context of chromatin organization. Dermato-Endocrinol 2011; 3: 125-9.
2. Sertznig P, Reichrath J. Peroxisome proliferator-activated receptors (PPARs) in dermatology: Challenge and promise. Dermato-Endocrinol 2011; 3:130-5.
3. Törmä H. Regulation of keratin expression by retinoids. Dermato-Endocrinol 2011; 3:136-40.
4. Melnik B. Isotretinoin and FoxO1: A scientific hypothesis. Dermato-Endocrinol 2011; 3:141-65.
5. Pérez P. Glucocorticoid receptors, epidermal homeostasis and hair follicle differentiation. Dermato-Endocrinol 2011; 3:166-74.
6. Schoepe S, Schäcke H, Asadullah K. Test systems for the determination of glucocorticoid receptor ligand induced skin atrophy. Dermato-Endocrinol 2011; 3:175-9.
7. Trémezaygues L, Reichrath J. Vitamin D analogs in the treatment of psoriasis: Where are we standing and where will we be going? Dermato-Endocrinol 2011; 3:180-6.
8. Sigmundsdottir H. From the bench to the clinic: New aspects on immunoregulation by vitamin D analogs. Dermato-Endocrinol 2011; 3:187-92.
9. Grant WB. A review of the role of solar ultraviolet-B irradiance and vitamin D in reducing risk of dental caries. Dermato-Endocrinol 2011; 3:193-8.
10. Grant WB. Effect of interval between serum draw and follow-up period on relative risk of cancer incidence with respect to 25-hydroxyvitamin D level; implications for meta-analyses and setting vitamin D guidelines. Dermato-Endocrinol 2011; 3:199-204.
11. Denzer N, Vogt T, Reichrath J. Vitamin D receptor (VDR) polymorphisms and skin cancer: A systematic review. Dermato-Endocrinol 2011; 3:205-10.
12. Safer JD. Thyroid hormone action on skin. Dermato-Endocrinol 2011; 3:211-5.