Psoriasis responds favourably to treatment with retinoids but the cellular pathways mediating these effects are poorly understood. Retinoids regulate keratinocyte proliferation and maturation via binding to nuclear retinoic acid receptors (mainly RARα and RARγ) which form heterodimers with the 9-cis-RA receptor, RXRα. We have previously shown that mRNA expression of RARα and RXRα is down-regulated in psoriatic lesions as compared with non-lesional human skin. In the present study, we investigated the protein expression of RARα, RARγ and RXRα in normal and psoriatic skin using indirect immunofluorescence analysis. Epidermal keratinocytes of normal and non-lesional psoriatic skin displayed similar nuclear localization of all three receptors; RARα was detected with decreasing intensity from basal to suprabasal layers, RARγ showed the opposite trend, whereas RXRα was evenly expressed throughout the epidermis. In lesional psoriatic skin, however, all three receptor proteins showed a much higher staining intensity in the lower half of the epidermis; in particular, RARα immunoreactivity was low or even absent in the upper layers of epidermis. The results support the idea that psoriasis is associated with abnormal retinoid signalling in lesional epidermis. Key words: psoriasis; retinoid receptor; retinoic acid; keratinocyte; epidermis.

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Synthetic retinoids and their endogenous counterpart, all-trans-retinoic acid (RA), have profound influence on the function of epidermal keratinocytes both in vitro and in vivo. This characteristic is exploited in the treatment of psoriasis, a genetic disease characterized by epidermal hyperproliferation, disturbed differentiation, and skin inflammation.

Once internalized, retinoids bind to cytoplasmic proteins [cellular retinol-binding protein (CRBP) or cellular retinoid acid-binding protein (CRABPI and II)] and nuclear retinoic acid receptors (RARα, -β and -γ), which are believed to mediate the genomic effects of retinoids (1). A second class of retinoid receptors, RXRα, -β and -γ, are activated by 9-cis-RA and phytanic acid, and function as auxilliary heterodimerization partners for RARs, as well as for the vitamin D receptor, liver X receptors, peroxisome proliferator-activated receptors (PPARs) and other members of a superfamily of nuclear receptors (1). The retinoid-activated RAR-RXR heterodimers recognize and bind to RA-response elements (RAREs) in the promoter region of certain genes, thereby recruiting co-activators leading to transcriptional induction of the adjacent gene (1). Retinoids may also interact with other signalling pathways, e.g. activator protein-1 (AP-1), which has been put forward as a key transcriptional regulator in the expression of many marker genes of keratinocyte differentiation. In addition, non-genomic effects have recently been implicated in the mechanism of action of retinoids in keratinocytes (2).

Human epidermal keratinocytes express three major retinoid receptor proteins, in the following order of abundance: RXRα > RARγ > RARα (3). According to some investigators, the receptors are mainly expressed in the upper layers of normal epidermis (4, 5) suggesting that they are involved in the process of terminal differentiation. In fact, altered retinoid receptor expression appears to be linked to aberrant growth and differentiation of epidermal keratinocytes; hence reduced retinoid receptor levels were found in mouse skin exposed to tumour promoters and human skin exposed to UV irradiation (6–8) as well as in human squamous cell carcinoma (9–11). Furthermore, a recent study in man showed progressive suppression of RAR and RXR expression going from a normal skin phenotype to premalignant actinic keratoses and invasive squamous cell carcinoma (5).

Valuable insight into the physiological role of retinoid receptors has come from experiments in transgenic mice. For example, developmental defects reminiscent of postnatal vitamin A deficiency were found in RARα-null mice (12, 13). A main conclusion from these experiments was that a functional redundancy exists between various RARs, which may allow for one type of receptor to compensate for a missing one. Also, targeted ablation of RAR-mediated signalling in basal keratinocytes leads to abnormal epidermal maturation (14), whereas selective disruption
of RARα results in abnormal lipid composition of stratum corneum and increased trans-epidermal water loss (15, 16), mimicking the situation in psoriatic lesions (17). Moreover, epidermal RXRα knock-out mice exhibit several skin abnormalities with striking similarities to psoriatic phenotype (e.g. hyperproliferation, thickened stratum corneum and inflammatory cell infiltrates) (18).

In a recent study using a quantitative PCR assay, we have shown that the mRNA expression of RARα and RXRα is markedly reduced in lesional skin as compared with non-lesional skin in psoriasis patients (19). In the present study, we have investigated RARα, RARγ and RXRα protein expression in normal and psoriatic skin biopsies using rabbit polyclonal antibodies and immunofluorescence analysis.

MATERIALS AND METHODS

Biological specimens

Nine patients with chronic and stable plaque psoriasis (eight men, one woman, aged 20–68 years) and nine healthy volunteers (six men, three women, aged 37–83 years) gave written consent to participate in the study approved by the Ethics Committee of Uppsala University. Except for their skin disorder, the patients were healthy and had not received any systemic or topical psoriasis therapy (excluding emollients) for at least 2 weeks prior to sampling. After infiltrating the skin with lidocaine (Xylocaine®, Astra, Sweden), 3-mm punch biopsies were obtained from normal skin (forearm or buttock) and non-lesional (buttock) plus lesional (periphery of nummular lesion of the trunk) skin in psoriasis patients.

Punch biopsies were immediately placed in cold Histocon tissue transport medium (Histolab Products AB, Gothenburg, Sweden), snap-frozen in isopentane and stored at −70°C.

Immunofluorescence procedure

The biopsies were cryo-sectioned (6 µm) and incubated with rabbit polyclonal subtype-specific retinoid receptor antibodies [RARα (C-20), RARβ (C-19), RARγ (C-19) or RXRα (D-20); Santa Cruz Biotechnologies, Inc., Santa Cruz, CA, USA] overnight at 4°C in a humidified chamber.

The specificity of the antibodies had been checked beforehand on Western blot analysis of nuclear extracts prepared from cultured normal human keratinocytes. The antibodies against RARα, RARγ and RXRα showed one major band with appropriate molecular weight (data not shown), whereas no band was discerned using the RARβ antibody, thus confirming the absence of RARβ in keratinocytes (4).

The antibodies were used at 1:200, 1:50, 1:400 and 1:800 dilution, respectively. After washing in phosphate-buffered saline, bound immunoglobulins were exposed to biotinylated anti-rabbit IgG secondary antibody for 1 h, and then to Texas Red® Avidin D (both from Vector Laboratories, Inc., Burlingame, CA, USA) for 30 min. A goat polyclonal Ku-86 antibody (M-20 at 1:200 dilution; Santa Cruz Biotechnologies) and biotinylated anti-goat IgG secondary antibody was used as positive control of a protein with known nuclear expression. Slides were mounted in Vectashield® Mounting Media (Vector Laboratories) containing Hoechst 33258 nuclear stain.

Microscopic analysis

Tissue sections were examined at ×20 magnification using a Leica DMRB microscope equipped with filters for detection of Texas Red (rhodamine) and Hoechst dye fluorescence. Digital images including overlays were captured using Leica QWin version 2.5 software (Leica Imaging Systems Ltd, Cambridge, UK). Texas Red (= RAR and RXR) fluorescence in three epidermal compartments (basal, spinous and granular layer) was scored from 0 to 3 as follows: 0, negative (no receptor-positive nuclei); 1, weak (few nuclei positive); 2, moderate (most nuclei positive); and 3, strong (all nuclei positive). Three microscopists independently evaluated all biopsies blindly.

Statistical analysis

Non-parametric Kruskal-Wallis one-way analysis and Dunn’s post-test (analogous to a Bonferroni test) were performed using the GraphPad Prism (version 2.0) software (San Diego, CA, USA).

RESULTS

Expression patterns in normal skin

Immunofluorescence staining of RARα, RARγ and RXRα in healthy control epidermis displayed receptor-positive nuclear immunoreactivity with no or weak cytoplasmic localization (Fig. 1a, c, d). As expected, no RARβ fluorescence was observed (Fig. 1b). The nuclear localization of the three former receptors and Ku-86 is further illustrated in Fig. 2 (left panel). When data from all nine controls were compiled, using a scoring system for receptor staining at three different layers of epidermis (Fig. 3a), it emerged that the RARα expression in normal epidermis was strongest in basal keratinocytes and decreased in suprabasal direction, RARγ was more intensely stained in suprabasal layers, whereas RXRα was more uniformly distributed across the epidermis with virtually all suprabasal nuclei being positive (Table I; Fig. 4).

Epidermal cells of the hair follicle and sebaceous gland showed strong RARα and RXRα fluorescence. In particular the peripheral (undifferentiated) sebocytes showed more intense signalling than the central (mature) ones. By contrast, RARγ and RARβ were weakly expressed by hair follicle keratinocytes and not at all by sebocytes (Fig. 1e–l). This differs from the results of Reichrath et al. (4) who, using a different source of antibody, found a strong RARγ expression in keratinocytes of the outer root sheath and sebaceous glands.

A strong nuclear RARα fluorescence was consistently found in dermal fibroblasts (Fig. 1a), endothelial cells and cells of the eccrine sweat glands (Fig. 1m, n). All these cell types were negative for RARβ and RARγ and only weakly positive for RXRα (results not shown). Negative controls, in which the primary antibody was excluded, showed no staining of the tissue sections (not shown).
Expression patterns in psoriatic skin

Immunofluorescence imaging and scoring of RARα, RARβ, RARγ and RXRα in non-lesional skin displayed no difference compared with healthy control skin (Figs 2 and 4; Table I).

In lesional psoriatic skin, all three receptor proteins were most conspicuous in the lower half of the epidermis (Figs 2, 3b and 4; Table I). This was especially true for RARγ and RXRα, both of which showed an opposite distribution compared with normal and non-lesional skin, with only weak receptor expression in the superficial layer. Similarly, RARα staining was sparse or absent at this level of lesional epidermis. In contrast, a normal distribution of RXRα was found in nickel-induced acute eczema, another inflammatory skin disease (data not shown).

The staining pattern of Ku-86, a non-receptor nuclear protein used as positive control, was similar in lesional compared to non-lesional psoriatic and normal skin (Fig. 2).

DISCUSSION

Our results show for the first time that the various nuclear retinoid receptor proteins exhibit individual expression patterns in normal human epidermis. Thus, whereas RARγ and RXRα were expressed throughout the entire epidermis, RARα showed strongest staining in basal nuclei with decreasing intensity in suprabasal direction. The latter finding is in contrast with the weak in situ hybridization signal for RARα previously demonstrated in basal keratinocytes (5), but supports our recent finding that RARα mRNA and protein expression is higher in undifferentiated versus differentiated keratinocytes in culture (Karlsson et al., unpublished observations).
In psoriatic skin, although the expression pattern was essentially normal in uninvolved skin, strikingly abnormal distribution of the three prominent receptors was found in lesional skin. In particular, RAR\( \alpha \) and RXR\( \alpha \) showed markedly reduced or even absent staining in superficial epidermis, corresponding to the granular layer in normal skin. This coincides with our previous finding of \( \geq 50\% \) reduced mRNA expression level for RAR\( \alpha \) and RXR\( \alpha \) in lesional versus non-lesional psoriatic skin (19). Other investigators have come to somewhat diverging conclusions. No differences in RAR\( \alpha \) and RXR\( \alpha \) mRNA between normal and lesional skin were detected by Northern blot analysis (20), and immunohistochemical and immunoblotting studies have either shown normal (21) or only slightly reduced (22) RXR\( \alpha \) expression in lesional psoriatic epidermis. The reason for this discrepancy is not known, but could result from using different sources of antibodies and different techniques for quantitation.

The reduced expression of retinoid receptors in superficial psoriatic lesions found in the present study is most likely a consequence of low mRNA levels. However, increased degradation of the receptor proteins is another option. One of the hallmarks of psoriasis is infiltration of inflammatory cells in epidermis and hence increased levels of pro-inflammatory cytokines such as IFN\( \gamma \) (see ref. 23 and references therein). In adipocytes, IFN\( \gamma \) is known to induce ubiquitin-proteasome-mediated degradation of PPAR\( \gamma \), another ligand-activated nuclear hormone receptor (24). This pathway has also been implicated as the major degradation route for retinoid receptors in keratinocytes (25). Our preliminary experiments indicate that IFN\( \gamma \) induces degradation of RAR\( \gamma \) and RXR\( \alpha \) protein in keratinocytes \textit{in vitro}, and that proteasome inhibitors efficiently block this process (Karlsson et al., unpublished observations). However, a recent immunohistochemical study showed that PPAR\( \alpha \) and PPAR\( \gamma \) exhibit a strong nuclear localization in superficial psoriatic epidermis (26), i.e. opposite to the RAR/RXR expression.

Whatever the cause is of the low levels of retinoid

\[ \text{Fig. 2. Nuclear distribution of RAR}\alpha, \text{RAR}\gamma \text{ and RXR}\alpha \text{ in normal skin and psoriatic non-lesional and lesional skin. Cryostat sections were incubated with polyclonal antibodies against RAR}\alpha, \text{RAR}\gamma, \text{RXR}\alpha \text{ or Ku-86 (diluted 1:200, 1:400, 1:800 and 1:200, respectively) and studied by \textit{in situ} immunofluorescence as described in Materials and Methods. Images in pairs: left, receptor detection by Texas Red-staining technique; right, overlay image of Texas Red and Hoechst 33258 (nuclei, blue) staining. Co-localized staining appears in pink. The intense red band present in some images is due to non-specific Texas Red staining of stratum corneum (also seen in Fig. 1e and g). Representative results from one healthy donor and one patient. Note the attenuated staining in superficial psoriatic skin. Scale bar: 30 \mu m.} \]
receptors in superficial psoriatic epidermis, this abnormality is likely to have biological consequences. One way of incriminating reduced RAR\(\gamma\) and RXR\(\alpha\) expression in the pathogenesis relates to the AP-1 signalling pathway. Interference with this transcription factor explains many of the biological effects of retinoids (27), and a correct balance between AP-1 and RAR/RXR signalling is probably crucial for normal keratinocyte differentiation. AP-1 is regarded as a key transcriptional regulator in the expression of several keratinocyte proteins associated with differentiation (e.g. keratin 1, transglutaminase 1, loricrin and involucrin) and proliferation (e.g. keratins 6 and 16), (see ref. 28 for review). In addition, AP-1 promotes the expression of genes involved in inflammation (23). Many of these genes are up-regulated in psoriatic lesions but can be repressed by anti-psoriatic retinoids such as RA and tazarotene (23). In theory, reduced

![Fig. 3. Schematic illustration of the subdivision of normal or non-lesional skin (a) and lesional psoriatic skin (b) into three epidermal cell layers: BL, basal layer (arrows); SpL, spinous layer; and GrL, granular layer. Although the granular layer per se is often absent in psoriatic lesional epidermis, this designation was consistently used to describe the most superficial layer of viable epidermis. Hoechst 33258 staining. Scale bar: 30\(\mu\)m.](image)

| Table I. Semi-quantitative assessment of retinoid receptor expression in normal skin, non-lesional and lesional psoriatic skin |
|---------------------------------|----------------|----------------|
| **Normal skin \((n=9)\)**       | **Psoriatic non-lesional skin \((n=9)\)** | **Psoriatic lesional skin \((n=9)\)** |
| **RAR\(\alpha\)**               | **Score**     | **Score**     | **Score**     |
| BL                              | 0 1 2 3       | 0 1 2 3       | 0 1 2 3       |
| SpL                             | 0 0 1 8       | 0 0 2 7       | 0 0 5 4       |
| GrL                             | 0 2 5 2       | 0 1 8 0       | 5 4 0 0       |
| **RAR\(\gamma\)**              | **Score**     | **Score**     | **Score**     |
| BL                              | 0 0 7 2       | 0 2 5 2       | 0 0 3 6       |
| SpL                             | 0 0 4 5       | 0 0 4 5       | 0 0 3 6       |
| GrL                             | 0 0 3 6       | 0 0 6 3       | 1 6 2 0       |
| **RXR\(\alpha\)**              | **Score**     | **Score**     | **Score**     |
| BL                              | 0 0 3 6       | 0 0 5 4       | 0 0 8 1       |
| SpL                             | 0 0 2 7       | 0 0 1 8       | 0 1 1 7       |
| GrL                             | 0 0 2 7       | 0 1 2 6       | 1 6 2 0       |

\(^a\)Three microscopists independently and blindly scored the immunofluorescence staining intensity from 0 to 3, and the median value was used to categorize the staining in different layers of each sample. Data represent number of samples falling into each staining category. BL, basal layer; SpL, spinous layer; GrL, granular layer (see Fig. 3 for explanation).
expression of retinoid receptors in psoriatic epidermis might allow for excessive AP-1 signalling and thus disturbed keratinocyte maturation.

Another theory incriminating reduced RAR/RXR levels in the pathogenesis of psoriasis involves the RA-inducible gene for CRABPII, which is strongly up-regulated in psoriatic lesions (29, 30). In contrast to normal skin, which responds to topical RA by increasing the CRABPII expression, psoriatic epidermis fails to do so (29); it compares in this respect to cultured normal keratinocytes also expressing low amounts of nuclear retinoid receptors (31). In keeping with these findings, it was recently shown that topical RA fails to induce CRABPII expression in the epidermis of dominant-negative RARα mutants (15). Under basal conditions, these animals show an unexpected twofold increase in CRABPII mRNA expression, thus resembling the situation in psoriatic epidermis. Di et al. (31) have proposed a scenario in which RAR-deficient cells, by some yet unknown mechanism, ‘sense’ their unresponsiveness to RA and try to compensate for this by up-regulating the CRABPII expression. CRABPII has been identified in the nucleus of several cell types (29, 32) and over-expression of the CRABPII protein enhances RA-mediated transcriptional activation (33, 34). A reduced expression of RAR/RXR in upper epidermis leading to increased CRABPII expression could thus paradoxically result in increased retinoid signalling in psoriatic keratinocytes with well-known effects of hyperproliferation and de-differentiation.

In conclusion, lesional psoriatic epidermis shows abnormal distribution profiles for RARα, RARγ and RXRα characterized by suppressed protein expression in superficial epidermis. Speculatively, this leads to aberrant retinoid signalling and a dysregulation of differentiation in psoriatic epidermis.

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REFERENCES

1. Giguère V. Retinoic acid receptors and cellular retinoid binding proteins: complex interplay in retinoid signaling. Endocrin Rev 1994; 15: 61–79.
2. Louafi F, Stewart CE, Perks CM, Thomas MG, Holly JM. Role of the IGF-II receptor in mediating acute, non-genomic effects of retinoids and IGF-II on keratinocyte cell death. Exp Dermatol 2003; 12: 426–434.
3. Fisher G, Talwar H, Xiao J-H, Datta S, Reddy A, Gaub M-P, et al. Immunological identification and functional quantitation of retinoic acid and retinoid X receptor proteins in human skin. J Biol Chem 1994; 269: 20629–20635.
4. Reichrath J, Mittmann M, Kamradt J, Muller SM. Expression of retinoid-X receptors (α-2, β-3, γ-1) and retinoic acid receptors (α-2, β-3, γ-1) in normal human skin: an immunohistological evaluation. Histochem J 1997; 29: 127–133.
5. Xu XC, Wong WY, Goldberg L, Baer SC, Wolf JE, Ramsdell WM, et al. Progressive decreases in nuclear retinoid receptors during skin squamous carcinogenesis. Cancer Res 2001; 61: 4306–4310.
6. Wang Z, Boudjelal M, Kang S, Voorhees JJ, Fisher GJ. Ultraviolet irradiation of human skin causes functional vitamin A deficiency, preventable by all-trans retinoic acid pre-treatment. Nat Med 1999; 5: 418–422.
7. Darwiche N, Scita G, Jones C, Rutberg S, Greenwald E, Tenenbaum T, et al. Loss of retinoic acid receptors in mouse skin and skin tumors is associated with activation of the ras(Ha) oncogene and high risk for premalignant progression. Cancer Res 1996; 56: 4942–4949.
8. Kumar R, Shoemaker AR, Verma AK. Retinoic acid nuclear receptors and tumor promotion: decreased expression of retinoic acid nuclear receptors by the...
tumor promoter 12-O-tetradecanoylphorbol-13-acetate. Carcinogenesis 1994; 15: 701 – 705.

9. Lotan RM. Squamous differentiation and retinoids. Cancer Treat Res 1995; 74: 43 – 72.

10. Darwiche N, Celli G, Tennenbaum T, Glick AB, Yuspa SH, DeLuca LM. Mouse skin tumor progression results in differential expression of retinoic acid and retinoid x receptors. Cancer Res 1995; 55: 2774 – 2782.

11. Monzon RI, Fillmore C, Hudson LG. Functional consequences of reduced retinoic acid receptor gamma expression in a human squamous cell carcinoma line. Mol Pharmacol 1997; 51: 377 – 382.

12. Lufkin T, Lohnes D, Mark M, Dierich A, Narumiya S, et al. High postnatal lethality and testis degeneration in retinoic acid receptor alpha mutant mice. Proc Natl Acad Sci U S A 1993; 90: 7225 – 7229.

13. Lohnes D, Kastner P, Dierich A, Mark M, Lemeur M, Chambon P. Function of retinoic acid receptor γ in the mouse. Cell 1993; 73: 643 – 658.

14. Saitou M, Sugai S, Tanaka T, Shimouchi K, Fuchs E, Narumiya S, et al. Inhibition of skin development by targeted expression of a dominant-negative retinoic acid receptor. Nature 1995; 374: 159 – 162.

15. Attar PS, Wertz PW, McArthur M, Imakado S, Bickenbach JR, Roop DR. Inhibition of retinoid signaling in transgenic mice alters lipid processing and disrupts epidermal barrier function. Mol Endocrinol 1997; 11: 792 – 800.

16. Imakado S, Bickenbach JR, Bundman DS, Rothnagel JA, Attar PS, Wang XJ, et al. Targeting expression of a dominant-negative retinoic acid receptor mutant in the epidermis of transgenic mice results in loss of barrier function. Genes Dev 1995; 9: 317 – 329.

17. Ghadially R, Reed JT, Elias PM. Stratum corneum structure and function correlates with phenotype in psoriasis. J Invest Dermatol 1996; 107: 558 – 564.

18. Li M, Chiba H, Warot X, Messaddeq N, Gerard C, Chambon P, et al. RXR-alpha ablation in skin keratinocytes results in alopecia and epidermal alterations. Development 2001; 128: 675 – 688.

19. Tömö H, Karlsson T, Michaelsson G, Rollman O, Vahlquist A. Decreased mRNA levels of retinoic acid receptor α, retinoid X receptor α and thyroid hormone receptor α in lesional psoriatic skin. Acta Derm Venereol 2000; 80: 4 – 9.

20. Elder JT, Fisher GJ, Zhang Q-Y, Eisen D, Krust A, Kastner P, et al. Retinoic acid receptor gene expression in human skin. J Invest Dermatol 1991; 96: 425 – 433.

21. Reichrath J, Munssinger T, Kerber A, Rochette-Egly C, Chambon P, Bahmer FA, et al. In situ detection of retinoid-X receptor expression in normal and psoriatic human skin. Br J Dermatol 1995; 133: 168 – 175.

22. Jensen T, Sørensen S, Sølvsten H, Kragballe K. The vitamin D3 receptor and retinoid X receptors in psoriatic skin: the receptor levels correlate with the receptor binding to DNA. Br J Dermatol 1998; 138: 225 – 228.

23. Thacher SM, Vasudevan J, Tsang KY, Nagpal S, Chandraratna RA. New dermatological agents for the treatment of psoriasis. J Med Chem 2001; 44: 281 – 297.

24. Floyd ZE, Stephens JM. Interferon-gamma-mediated activation and ubiquitin-proteasome-dependent degradation of PPARgamma in adipocytes. J Biol Chem 2002; 277: 4062 – 4068.

25. Boudjdelal M, Wang Z, Voorhees JJ, Fisher GJ. Ubiquitin/proteasome pathway regulates levels of retinoic acid receptor gamma and retinoid X receptor alpha in human keratinocytes. Cancer Res 2000; 60: 2247 – 2252.

26. Westergaard M, Henningsen J, Johansen C, Rasmussen S, Lyhne Svendsen M, Birke Jensen U, et al. Expression and localization of peroxisome proliferator-activated receptors and nuclear factor κB in normal and lesional psoriatic skin. J Invest Dermatol 2003; 121: 1104 – 1117.

27. Nagpal S, Athanikar J, Chandraratna RA. Separation of transactivation and AP1 antagonism functions of retinoic acid receptor α. J Biol Chem 1995; 270: 923 – 927.

28. Eckert RL, Crish JF, Banks EB, Welter JF. The epidermis: genes on – genes off. J Invest Dermatol 1997; 109: 501 – 509.

29. Karlsson T, Virtanen M, Sirsjo A, Rollman O, Vahlquist A, Tömä H. Topical retinoic acid alters the expression of cellular retinoic acid binding protein-I and cellular retinoic acid binding protein-II in non-lesional but not in lesional psoriatic skin. Exp Dermatol 2002; 11: 143 – 152.

30. Stiegenthaler G, Tomatis I, Didierjean L, Jaconi S, Saurat J-H. Overexpression of cellular retinoic acid binding protein type II (CRABP-II) and down-regulation of CRABP-I in psoriatic skin. Dermatology 1992; 185: 143 – 152.

31. Di W, Li XY, Datta S, Åström A, Chambon P, et al. Keratinocyte-specific retinoid regulation of human cellular retinoic acid binding protein-II (hCRABPII) gene promoter requires an evolutionarily conserved DR1 retinoic acid-responsive element. J Invest Dermatol 1998; 111: 1109 – 1115.

32. Gaub M-P, Lutz Y, Ghyselinck NB, Scheuer I, Pfister V, Chambon P, et al. Nuclear detection of cellular retinoic acid binding proteins I and II with new antibodies. J Histochem Cytochem 1998; 46: 1103 – 1111.

33. Delva L, Bastie JN, Rochette-Egly C, Kraiba R, Baltrands N, Despouy G, et al. Physical and functional interactions between cellular retinoic acid binding protein II and the retinoic acid-dependent nuclear complex. Mol Cell Biol 1999; 19: 7158 – 7167.

34. Dong D, Ruuska SE, Levinthal DJ, Noy N. Distinct roles for cellular retinoic acid-binding proteins I and II in regulating signaling by retinoic acid. J Biol Chem 1999; 274: 23695 – 23698.