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Expression of nerve growth factor and its high-affinity receptor, tyrosine kinase A proteins, in the human scalp skin

Background: Nerve growth factor (NGF) and its high-affinity receptor, tyrosine kinase A (TrkA), are members of the neurotrophin family. NGF–TrkA are involved in murine hair morphogenesis and cycling. To date, their expression in human hair follicle (HF) is unknown. In this investigation, we hypothesize that NGF–TrkA proteins are expressed in the human scalp skin. Moreover, NGF–TrkA expression in HF changes with the transitions from anagen→catagen→telogen stages.

Materials and methods: To test our hypothesis and to fill this existing gap in literature, the immunostaining values (semiquantitative evaluation of protein expression: SI, staining intensity; PP, percentage of positive cells; and IR score, immunoreactivity score) of NGF and TrkA proteins were examined in human scalp skin by immunofluorescent and immunoperoxidase staining methods. Fifty normal human scalp skin biopsy specimens were examined (healthy females, 53–57 years). In each case, 50 HFs were analyzed (35, 10, and five follicles in anagen, catagen, and telogen, respectively).

Results: The IR scores were statistically significantly higher ($p < 0.001$) in anagen as compared with either catagen or telogen HF (9.61 ± 0.12 vs. 1.4 ± 0.10 vs. 0.6 ± 0.10 for NGF and 3.31 ± 0.02 vs. 0.5 ± 0.10 vs. 0.2 ± 0.10 for TrkA). In the anagen HF, high expression values were seen in the distal region, followed by upper distal, lower distal, and bulb regions for both NGF (10.6 ± 0.21 vs. 10.3 ± 0.21 vs. 9.2 ± 0.40 vs. 8.1 ± 0.30) and TrkA (3.54 ± 0.07 vs. 3.45 ± 0.07 vs. 3.31 ± 0.06 vs. 3.13 ± 0.04). Both NGF and TrkA proteins showed prominent expression in the melanocytes (7.6 ± 0.15 vs. 2.50 ± 0.07), keratinocytes (10.2 ± 0.40 vs. 2.71 ± 0.06), sebaceous glands (10.2 ± 0.40 vs. 2.72 ± 0.06), and sweat glands (10.4 ± 0.40 vs. 2.84 ± 0.05).

Conclusions: Our findings report, for the first time, the expression pattern of NGF and TrkA proteins in human scalp skin and HF. The differential expression of these proteins during HF cycling suggests their possible roles in human HF biology. The clinical ramifications of these observations mandate further investigations.

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Mohamed A. Adly[1], Hanan A. Assaf[2], Essam A. Nada[2], Mohsen Soliman[3] and Mahmoud Hussein[4]

[1]Department of Zoology, Sohag Faculty of Science,
[2]Department of Dermatology and Venereology, Sohag Faculty of Medicine, South Valley University, Sohag,
[3]Department of Dermatology and Venereology, Faculty of Medicine, Cairo University, Giza, and
[4]Department of Pathology, Faculty of Medicine, Assiut University, Assuit, Egypt

Mahmoud R. Hussein, MD, PhD, Lecturer of Pathology, Consultant Pathologist, Department of Pathology, Faculty of Medicine, Assuit University Hospitals, Assuit University, Assuit, Egypt
Tel: +20 93 583 166
Fax: +20 88 333 327
e-mail: mrh17@swissinfo.org

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Neurotrophins (NTs), a family of structurally and functionally related proteins, are growth factors that act through binding to specific tyrosine kinase receptors. The nerve growth factor (NGF), a member of NT family, has a high-affinity receptor known as tyrosine kinase A (TrkA),[1] and together, they have roles in neuronal development. Recent studies suggest that NGF and Trk proteins also regulate tissue morphogenesis, remodeling, proliferation, and apoptosis.[2] Moreover, NGF and TrkA have several modulatory functions outside the nervous system.[3–5]

As both cutaneous epithelium and nervous system have a common neuroectodermal origin, it is conceivable that growth factors (such as NGF–TrkA) which control the development of the neurons are also involved in skin morphogenesis. Several observations support this proposition. First, the proliferation and survival of the melanocytes are affected by NTs.[6] Second, NGF is critical for proper innervation of the skin.[7] Therefore, defects in NGF signaling are associated with sensory cutaneous disorders resulting in ulcer formation.[8] Third, the skin, particularly the epidermis, is a rich source of NGF.[9,10] The epidermal keratinocytes are not only important NGF sources, but also NT targets expressing NT receptors.[11] Furthermore, NGF can stimulate proliferation and inhibits apoptosis in cultured human epidermal keratinocytes.[12] Lastly, in murine skin organ cultures, NGF is produced by the keratinocytes.[13] Alternatively, in mice, NGF expression increases in anagen with acceleration of hair follicle (HF) morphogenesis.[14,15] Taken collectively, it is possible that NGF and TrkA proteins are also involved in human scalp skin and HF biology. To date, the expression pattern of both NGF and TrkA proteins in the human scalp and HF is unknown.

In this investigation, we hypothesized that NGF–TrkA proteins are expressed in the human scalp skin. Moreover, NGF–TrkA protein expression in HF changes with the transitions from anagen→catagen→telogen stages. To test this hypothesis and to fill this existing gap in literature, we examined the immunostaining values of both NGF and TrkA proteins in human scalp skin by immunofluorescent and immunoperoxidase methods. Fifty normal human scalp skin biopsy specimens were examined (healthy females, 53–57 years). We addressed two questions: (1) what is the expression pattern of NGF and TrkA proteins in human scalp skin and HF? (2) What is the expression pattern of NGF and TrkA proteins in anagen, catagen, and telogen?

Materials and methods

Skin samples

Fifty normal human scalp skin specimens were obtained from 50 females (age: 53–57 years; after informed consent) undergoing elective cosmetic plastic surgery. None of these females have accompanying primary hair disorder. The specimens were obtained from both frontal and temporal regions of the scalp. After surgery, samples were maintained in Williams' Medium E (Biochrom KG Seromed, Berlin, Germany) for transportation at 4°C for up to 24 h. Skin specimens used for cryosections were abruptly frozen in liquid nitrogen and stored at −80°C until use. Before immunostaining, samples were embedded and processed for longitudinal cryosections (8 μm). Sections were dried, fixed in cold acetone (−20°C), and stored at −20°C until used for immunohistochemistry. Fifty HF (35 anagen, 10 catagen, and five telogen) were examined in each case. There were no remarkable immunohistological variations among these cases.

Immunohistochemistry

Cryosections of normal human scalp skin were immunostained using polyclonal rabbit antibody against human NGF (Santa Cruz Biotechnology, Santa Cruz, CA, USA) and polyclonal goat antibody against human TrkA (Santa Cruz Biotechnology). Two labeling techniques were performed to visualize antigen–antibody complexes: the avidin–biotin complex (ABC) labeling (Vector Laboratories, Burlingame, CA, USA) and the highly sensitive immunofluorescent tyramide signal amplification (TSA) labeling (PerkinElmer Life Science, Boston, MA, USA). For the ABC labeling method, cryosections of normal human scalp skin were washed in Tris-buffered saline (TBS, 0.05 M, pH 7.6) and preincubated with avidin–biotin blocking kit solution (Vector Laboratories), followed by incubation with protein-blocking agent (Immunotech, Krefeld, Germany) to prevent non-specific binding. Sections were then incubated with the primary antibodies diluted in TBS (NGF 1 : 100 and TrkA 1 : 50) containing 2% goat serum with NGF or 2% rabbit serum with TrkA, for 1 h at room temperature or overnight at 4°C. Thereafter, sections were incubated with biotinylated secondary antibodies goat anti-rabbit immunoglobulin G (IgG) and rabbit anti-goat IgG (Jackson ImmunoResearch Laboratories, West Grove, PA, USA) diluted 1 : 200 in TBS containing 2% goat and rabbit serum, respectively, for 30 min at room temperature. Next, sections were incubated with avidin–biotin–alkaline phosphatase complex (Vecta-Stain Kits; Vector Laboratories) diluted in TBS (1 : 100) for 30 min at room temperature. The alkaline phosphatase color reaction was developed by applying a staining protocols described before,[16–19] using fast red tablets (Sigma-Aldrich Chemie GmbH, Steinheim, Germany). Lastly, sections were

counterstained with Meyer's hematoxylin, covered with Kaiser glycerol (Dako, Denmark), and stored at 4°C for microscopic examination and analysis.

For TSA labeling technique, cryosections were washed in Tris acid–Tween buffer (TNT, pH 7.5), followed by washing in 3% hydrogen peroxide (H_2O_2). Sections were then incubated with lower concentrations of primary antibodies diluted in Tris acid-blocking buffer (TNB, pH 7.2, NGF 1 : 1000 and TrkA 1 : 500) overnight at 4°C. Next, sections were washed in TNT and incubated with tetramethylrhodamine isothiocyanate (TRITC)-conjugated F(ab)2 fragments of goat anti-rabbit IgG and rabbit anti-goat IgG secondary antibodies (Jackson ImmunoResearch Laboratories) diluted in TNB (1 : 200) for 30 min at room temperature. Thereafter, sections were incubated with streptavidin horseradish peroxidase (1 : 50 in TNB) for 30 min at room temperature. Finally, tetramethylrhodamine isothiocyanate–tyramide amplification reagent was administrated (1 : 50 in amplification diluent provided with the kit) for 30 min at room temperature, followed by counterstaining with 4′,6′-diamidino-2-phenylindole and mounting in levamisole (DAKO Corporation, Carpenteria, CA, USA). The TSA signals were visualized under a fluorescence microscope (Zeiss, Jena, Germany).

Positive control

The positive control specimens, for both NGF and TrkA, consisted of internal positive controls (melanocytes) and external positive controls (glial cells and neurons of the mouse cerebral cortex).

Negative control

Additional sections, running in parallel but with omission of the primary antibodies, served as the negative controls for both NGF and TrkA.[20]

Semiquantitation of NGF and TrkA protein expression

The immunoreactivity score (IR score) was evaluated by multiplying the percentage of positive cells (PP%) and the staining intensity (SI). First, the PP% was scored as 0 for <5%, 1 for 5–25%, 2 for 25–50%, 3 for 50–75%, and 4 for >75%. Second, the SI was scored as 1 for weak, 2 for medium, and 3 for intense staining, following other groups.[20,21]

Statistical analysis

Statistical comparison of the protein-expressing values among anagen, catagen, and telogen was evaluated using analysis of variance (ANOVA). Calculations were done with the statistical package SPSS for windows, version 10.0. Statistical significance was defined as $p < 0.05$.

Results

The positive (melanocytes and mouse brain tissue) and negative controls were positive and negative, respectively, indicating the validity of our results. The expression values of both NGF and TrkA proteins in the anagen were statistically significantly higher than that of either telogen or catagen ($p < 0.001$). Alternatively, the differences among the expression values of these proteins in the telogen and catagen did not reach the level of statistical significance ($p < 0.3$ and <0.6, respectively). High expression values were observed in the central region of the anagen, sebaceous, and sweat glands. A summary of these results is summarized in Table 1 and Figs 1–5.

NGF protein expression during anagen

In anagen HF (anagen VI), NGF staining values were higher than that of the other cycling stages; catagen and telogen (2.64 ± 0.02 vs. 0.7 ± 0.10 vs. 0.3 ± 0.10 for SI; 3.58 ± 0.26 vs. 1.9 ± 0.10 vs. 1.6 ± 0.10 for PP; and 9.61 ± 0.12 vs. 1.4 ± 0.10 vs. 0.6 ± 0.10 for IR score). Examination of the different regions of anagen HF (distal region vs. upper central region vs. lower central region vs. bulb region) revealed higher expression values in the distal region (2.9 ± 0.03 vs. 2.7 ± 0.06 vs. 2.6 ± 0.07 vs. 2.4 ± 0.06 for SI; 3.6 ± 0.06 vs. 3.5 ± 0.07 vs. 3.4 ± 0.07 vs. 3.3 ± 0.06 for PP; and 10.6 ± 0.21 vs. 10.3 ± 0.21 vs. 9.2 ± 0.40 vs. 8.1 ± 0.30 for IR score, respectively) (Table 1, Fig. 5). Moreover, NGF immunoreactivity was mainly detected in the ORS, IRS, DP, and CTS (Fig. 1A–I and the schematic representation 1). In the ORS, the immunostaining of NGF was different in the different regions of the follicle (Fig. 1). In the proximal cycling portion, NGF expression in ORS was strong in the suprabulbar region (Fig. 1A–C,F–H,J), slightly decreased toward the lower suprabulbar region until it absolutely disappeared in the lower portion of the bulb (Fig. 1E,I,J). In the lower suprabulbar regions, NGF immunoreactivity was prominent and strongest in the innermost (companion) layer but absent from the basal layer of the ORS (Fig. 1D,E,H,I). In the upper suprabulbar region, NGF immunostaining was strong in all layers, with increasing intensity toward the basal layer of the ORS (Fig. 1B,F,G,J). In the bulge and isthmus regions, NGF staining was confined to the basal and one to two outer suprabasal layers of

Table 1. Expression values of nerve growth factor (NGF) and its high-affinity receptor tyrosine kinase A (TrkA) in the human scalp skin and hair follicle

	NGF			TrkA		
	SI	PP	IR score	SI	PP	IR score
Anagen	2.64 ± 0.0	3.58 ± 0.2	9.61 ± 0.12	1.36 ± 0.02	1.57 ± 0.02	3.31 ± 0.02
Bulb region	2.4 ± 0.06	3.3 ± 0.06	8.1 ± 0.30	1.06 ± 0.03	1.27 ± 0.06	3.13 ± 0.04
Lower central region	2.6 ± 0.07	3.4 ± 0.07	9.2 ± 0.40	1.33 ± 0.06	1.49 ± 0.07	3.31 ± 0.06
Upper central region	2.7 ± 0.06	3.5 ± 0.07	10.3 ± 0.21	1.41 ± 0.06	1.54 ± 0.07	3.45 ± 0.07
Distal region	2.9 ± 0.03	3.6 ± 0.06	10.6 ± 0.21	1.58 ± 0.06	1.62 ± 0.06	3.54 ± 0.07
Catagen	0.7 ± 0.10	1.9 ± 0.10	1.4 ± 0.10	0.3 ± 0.10	0.6 ± 0.10	0.5 ± 0.10
Telogen	0.3 ± 0.10	1.6 ± 0.10	0.6 ± 0.10	0.1 ± 0.10	0.3 ± 0.10	0.2 ± 0.10
Sebaceous glands	2.7 ± 0.06	3.7 ± 0.06	10.2 ± 0.40	1.37 ± 0.06	1.70 ± 0.06	2.72 ± 0.06
Sweat glands	2.6 ± 0.06	3.8 ± 0.06	10.4 ± 0.40	1.50 ± 0.07	1.76 ± 0.05	2.84 ± 0.05
Keratinocytes	2.7 ± 0.06	3.7 ± 0.06	10.2 ± 0.40	1.29 ± 0.06	1.70 ± 0.06	2.71 ± 0.06
Melanocytes	2.5 ± 0.07	3.5 ± 0.07	7.6 ± 0.15	1.29 ± 0.06	1.49 ± 0.07	2.50 ± 0.07

The immunoreactivity score (IR score) was evaluated by multiplying the percentage of positive cells (PP%) and the staining intensity (SI). First, the PP% was scored as 0 for <5%, 1 for 5–25%, 2 for 25–50%, 3 for 50–75%, and 4 for >75%. Second, the SI was scored as 1 for weak, 2 for medium, and 3 for intense staining, following other groups.

keratinocytes (Fig. 1J). In the infundibulum, NGF immunopositivity was similar to that of the epidermis, being strongest in the basal layer and decreasing gradually toward the granular layer until it disappeared in the stratum corneum (Figs 1J and 2D,H). In the IRS, NGF expression was confined to the upper suprabulbar region (Fig. 1B–C,F–G,J).

NGF protein expression during catagen

During anagen–catagen transition and early catagen, the expression of NGF increased slightly compared to anagen VI. However, toward the mid- and late-catagen, NGF immunopositivity decreased dramatically and became moderately expressed in the involuting keratinocytes of

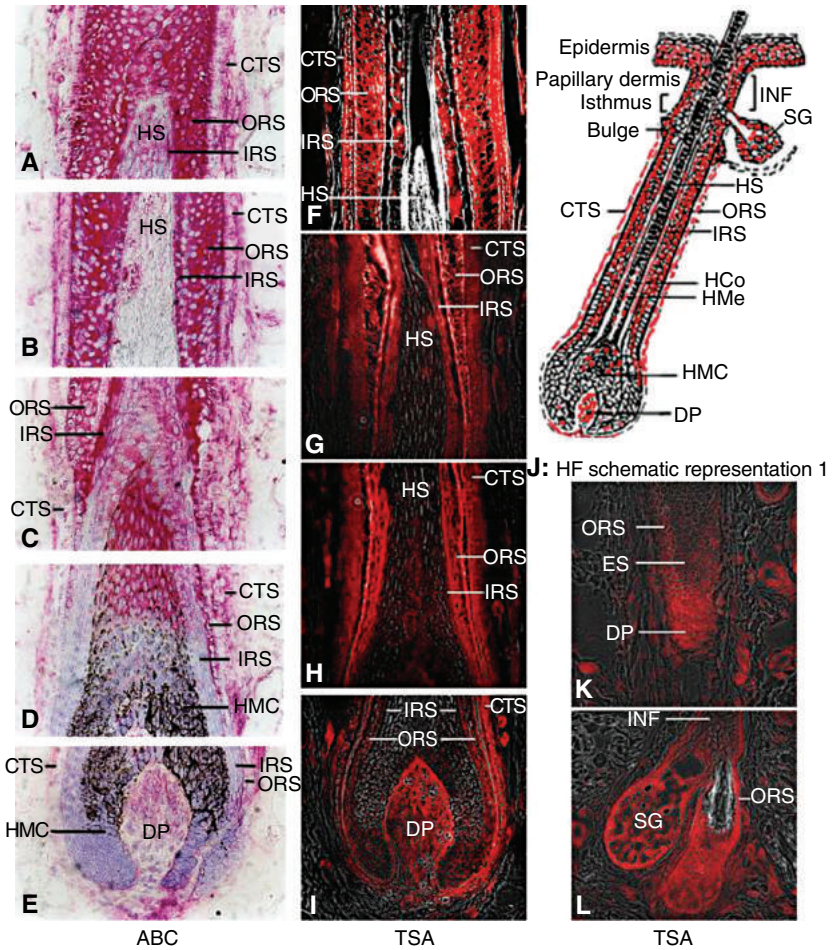

Fig. 1. Immunoreactivity of nerve growth factor (NGF) in human scalp HF, shown in red color with ABC and TSA techniques. A–E (panel 1) and F–I (panel 2) show expression in anagen VI HF. J is a schematic representation of anagen VI HF showing NGF expression in red color. K and L show expression in catagen and telogen HF, respectively.

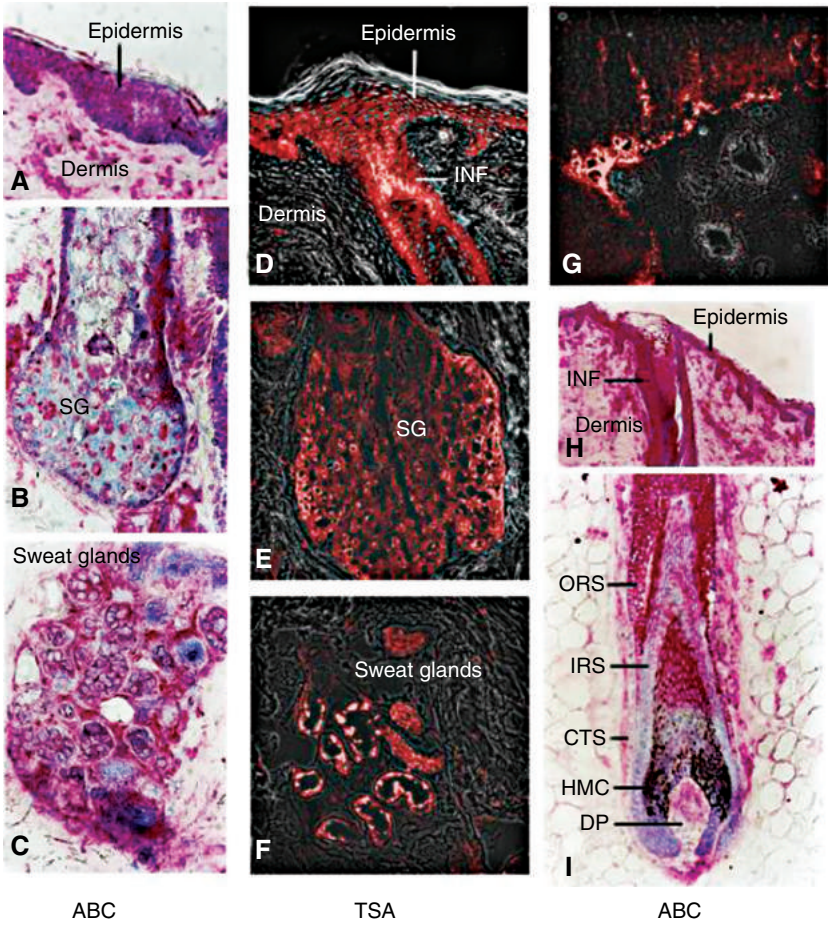

Fig. 2. Immunoreactivity of nerve growth factor (NGF) in human scalp skin and extrafollicular structures, shown in red color with ABC and TSA techniques. A and D show the epidermis. B and E show expression in the sweat gland (SG). C and F show expression in the SG. G shows a positive control of mouse cerebral cortex. H and I show expression in some fibroblasts in the dermis and adipocytes in subcutis.

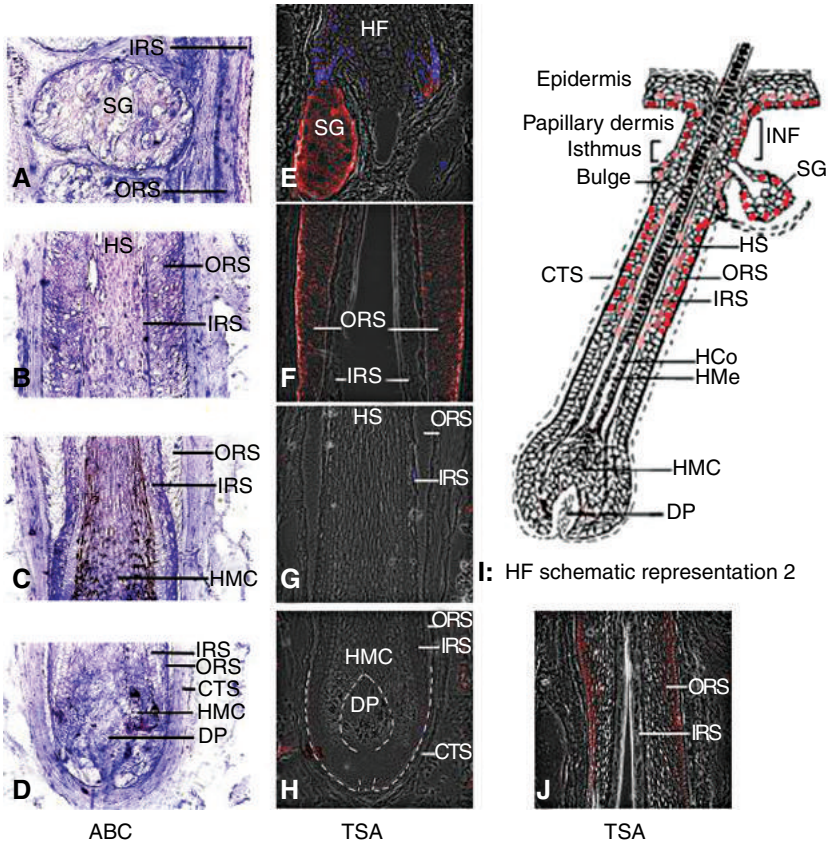

Fig. 3. Immunoreactivity of TrkA in human scalp HF, shown in red color with ABC and TSA techniques. A–D (panel 1) and E–H (panel 2) show expression in anagen VI HF. A and E also show expression in the SG. I is a schematic representation of anagen VI HF showing tyrosine kinase A (TrkA) expression in red color. J shows expression in catagen HF.

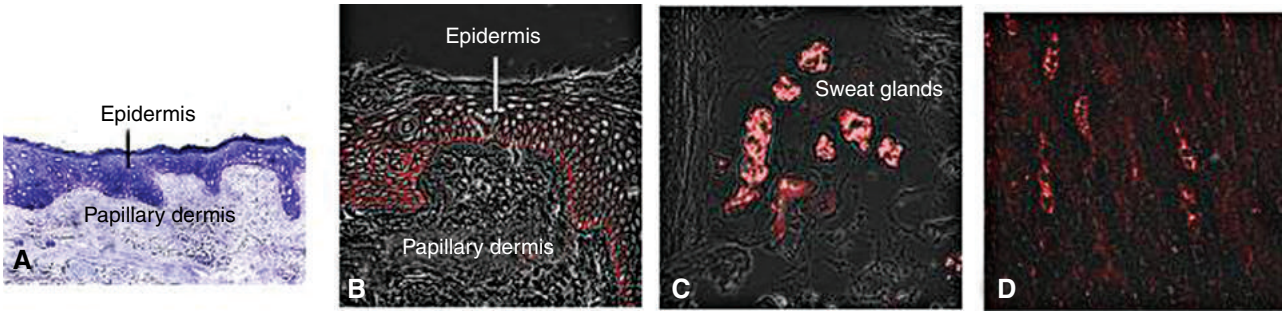

Fig. 4. Immunoreactivity of TrkA in human scalp skin and extrafollicular structures, shown in red color with ABC and TSA techniques. A and B show expression in the epidermis. C shows expression in the sweat gland. D shows a positive control of mouse cerebral cortex.

epithelial strand, but weakly expressed in the basal layer of the ORS during catagen VI (Fig. 1K).

NGF protein expression during telogen

In telogen HF and particularly in telogen–anagen transition, NGF expression increased moderately to include all layers of the ORS (Fig. 1L).

NGF protein expression in the epidermis and other extrafollicular structures

Outside from HF compartment, NGF expression was detected in the epidermis, sebaceous glands, sweat glands, and some fibroblasts in the dermis and adipocytes in the subcutis (Fig. 2A–F,H–I). The expression values in the sebaceous glands, sweat glands, keratinocytes, and melanocytes, respectively, were 2.7 ± 0.06 vs. 2.6 ± 0.06 vs. 2.7 ± 0.06 vs. 2.5 ± 0.07 for SI; 3.7 ± 0.06 vs. 3.8 ± 0.06 vs. 3.7 ± 0.06 vs. 3.5 ± 0.07 for PP; 10.2 ± 0.40 vs. 10.4 ± 0.40 vs. 10.2 ± 0.40 vs. 7.6 ± 0.15 for IR score (Table 1, Fig. 5). In the epidermis, NGF expression was found in all layers except stratum corneum that had only a very weak expression or was absolutely negative (Fig. 2A,D). NGF expression was strongest in the basal layer and decreased gradually toward the granular layer. In sebaceous glands, NGF showed a prominent expression, especially in the peripheral sebaceocytes (Fig. 2B,E). In sweat glands, NGF was strongly expressed (Fig. 2C,F).

TrkA protein expression during anagen

In anagen HF (anagen VI), TrkA staining values were higher than those of the other cycling stages; catagen and telogen (1.36 ± 0.02 vs. 0.3 ± 0.10 vs. 0.1 ± 0.10 for SI; 1.57 ± 0.02 vs. 0.6 ± 0.10 vs. 0.3 ± 0.10 for PP; and 3.31 ± 0.02 vs. 0.5 ± 0.10 vs. 0.2 ± 0.10 for IR score). Examination of the different regions of anagen HF (distal region vs. upper central region vs. lower central region vs. bulb region) revealed higher expression values in the distal region (1.58 ± 0.06 vs. 1.41 ± 0.06 vs. 1.33 ± 0.06 vs. 1.06 ± 0.03 for SI; 1.62 ± 0.06vs. 1.54 ± 0.07 vs. 1.49 ± 0.07 vs. 1.27 ± 0.06 for PP; and 3.54 ± 0.07 vs. 3.45 ± 0.07 vs. 3.31 ± 0.06 vs. 3.13 ± 0.04 for IR score, respectively) (Table 1, Fig. 5). The expression values in the anagen were statistically significantly higher than that of either the telogen or catagen ($p < 0.001$). Alternatively, the differences between the expression values in the telogen and catagen did not reach the level of statistical significance ($p < 0.6$). A summary of these staining values is presented in Table 1 and Fig. 5. In anagen HF (anagen VI), the immunoreactivity of TrkA was mainly detected in the ORS and IRS. In ORS, TrkA immunostaining was detected in the upper suprabulbar region, with prominent expression in the basal layer and intermediate expression in suprabasal keratinocytes distributed sporadically in the ORS (Fig. 3B,F and the schematic representation 2). In the bulge and isthmus regions, TrkA protein was expressed only in the basal layer (Fig. 3A,E,I). In the infundibulum, TrkA immunostaining was similar to that of the epidermis and was detected in the basal layer and one to two suprabasal layer (Figs 3I and 4B).

TrkA protein expression during catagen and telogen

In catagen HF, particularly early- and mid-catagen, TrkA immunostaining was seen in the basal layer of the upper proximal ORS (Fig. 3J). In telogen HF, TrkA was weakly expressed.

TrkA protein expression in the epidermis and other extrafollicular structures

In the epidermis, TrkA immunoreactivity was shown in the basal layer and two to three suprabasal

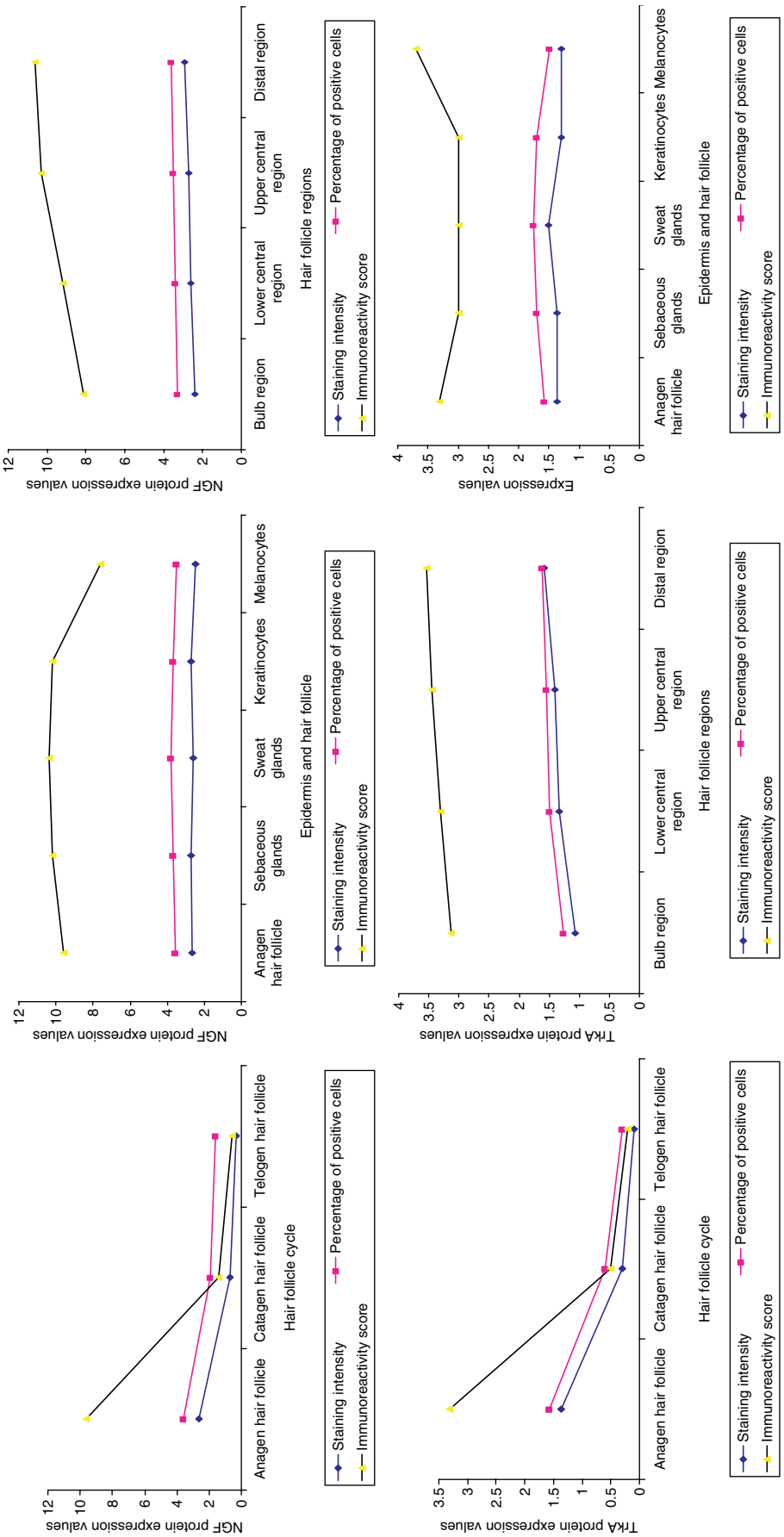

Fig. 5. Immunostaining values of NGF–TrkA proteins in the human scalp skin and hair follicles.

layers (Figs 3I and 4A,B). In the sebaceous glands, TrkA was prominently expressed (Fig. 3A,E). In the sweat glands, a strong expression of TrkA was also found (Fig. 4C). No TrkA immunoreactivity was found in the dermis or subcutis. The expression values in the sebaceous glands, sweat glands, keratinocytes, and melanocytes, respectively, were 1.37 ± 0.06 vs. 1.50 ± 0.07 vs. 1.29 ± 0.06 vs. 1.29 ± 0.06 for SI; 1.70 ± 0.06 vs. 1.76 ± 0.05 vs. 1.70 ± 0.06 vs. 1.49 ± 0.07 for PP; and 2.72 ± 0.06 vs. 2.84 ± 0.05 vs. 2.71 ± 0.06 vs. 2.50 ± 0.07 for IR score (Table 1, Fig. 5). All the figures (Figs 1–5) were representative of TrkA immunoreactivity in the entire group of biopsies.

Discussion

To date, the expression of NGF–TrkA proteins in human HF is still unknown. In this investigation, we hypothesized that NGF–TrkA proteins are expressed in the human scalp skin. We further hypothesized that the expression of these proteins in HF changes with the transitions from anagen→catagen→telogen stages. To fill this existing gap in literature and to test our hypothesis, we carried out this investigation. Our study clearly demonstrated the following observations: (i) NGF–TrkA proteins are expressed in normal human scalp skin; (ii) HF cycling transitions are associated with alterations in the expression of NGF and TrkA proteins; (iii) strong expression of NGF–TrkA proteins occurs in the anagen whereas weak reactivity occurs in catagen and telogen HF; and (iv) NGF and TrkA proteins are strongly expressed in the sweat, sebaceous glands, keratinocytes, and melanocytes.

NGF–TrkA proteins are expressed in normal human scalp skin

This study reports, for the first time, that both NGF and TrkA proteins are expressed in the human scalp skin. The expression of these proteins in normal human skin suggests that the NGF–TrkA system may operate as an additional neuronal signaling pathway regulating skin functions. Since NGF is a regulator of TrkA gene expression, it is conceivable that the increased content of NGF in anagen IV is functionally linked to synthesis of the TrkA protein in the skin.[22] In support, there is indeed hair cycle-dependent expression of TrkA protein in the human scalp skin. Although the exact source of these proteins is unknown, we propose that they may originate from either cutaneous or extracutaneous sites of synthesis. The former include epithelial cells, fibroblasts, and Merkel cells. The extracutaneous sources include delivery to skin via descending nerve endings.[23] This possibility is supported by the presence of NGF and TrkA proteins in nerve bundles of dermis and subcutis. Also, some NGF and TrkA proteins may derive from the serum. It is still possible that some of NGF and TrkA proteins are the product of an as yet unidentified cutaneous genes whose products have high homology to brain NGF–TrkA.[4]

Hair follicle cycling transitions are associated with alterations in the expression of NGF and TrkA proteins

In our series, the distribution of NGF–TrkA proteins changes in a hair cycle-dependent manner. The NGF and TrkA protein immunoreactivities were weak in catagen/telogen skin and reached its highest value in anagen VI. These findings indicate that HF cycling is associated with alterations in the expression of these proteins. They also agree with previous studies showing altered NGF protein level in C57BL/6 mouse HF in a hair cycle-dependent manner.[24] The high expression values of NGF and TrkA proteins in anagen HF indicate possible roles for these proteins in human HF cycling changes. The possible mechanisms by which NGF can share to anagen development include its ability to promote reparative angiogenesis and inhibit endothelial apoptosis. In support, NGF protein has a reparative action during the healing of the cutaneous wounds in diabetic mice. In this regard, NGF can correct endogenous liabilities, facilitate vascular regeneration, and suppress endothelial apoptosis.[25] Also, it is still possible that NGF can combat apoptosis in the anagen by suppression of caspase-12 activity.[26] Interestingly, NGF is the target of many therapeutic agents such as cyclosporin A, steroids, and estrogen.[27,28] Thus, our observations raise questions about the possible therapeutic ramifications for NGF receptor agonists and antagonists in the treatment of HF disorders such as alopecias and hirsutism.

Expression of NGF–TrkA proteins in sweat glands, sebaceous glands, melanocytes, and keratinocytes

The strong expression of NGF–TrkA proteins in the keratinocytes, melanocytes, sebaceous glands, and sweat glands may be reasoned to a predominantly receptor-mediated internalization of NGF–TrkA proteins released by nerve endings. The expression of NGF and TrkA in human epidermal keratinocytes not only concurs similar findings in murine keratinocytes[13] but also suggests their possible roles in regulating the growth kinetics of these cells. Also, these findings suggest that NGF–TrkA-mediated signaling is critical for the health and diseases of these structures. A functional TrkA protein is essential for

NGF signaling.[29] Therefore, TrkA gene mutations can result in signaling defects including the inability of NGF to induce TrkA phosphorylation. These NGF–TrkA signaling defects may help explain some of the sweat gland disorders such as congenital insensitivity to pain with anhidrosis syndrome. Also, in acne vulgaris, increased expression of NGF was seen in the germinative cells of the sebaceous glands. Therefore, it is possible that downregulation of NGF might be useful in the treatment of this condition.[30]

Here we show by immunohistological staining methods the expression pattern of NGF and TrkA proteins in HF and epidermis of the human skin. We report that the distribution of NGF and TrkA proteins changes in a hair cycle-dependent manner. The NGF and TrkA protein immunoreactivities were weak in catagen/telogen skin and reached its highest value in anagen VI. Also, protein immunoreactivities were found in the keratinocytes, melanocytes, sweat, and sebaceous glands. The possible clinical ramifications of these findings are open for further investigations.

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