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NEUROTROPHINS AND THEIR RECEPTORS IN THE SKIN: A TRIBUTE TO RITA LEVI-MONTALCINI

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The family of proteins named neurotrophins and also their receptors play an important role in differentiation and survival of specific populations of neurons, including cutaneous nerves. Recent advance in neuroscience has shown that in addition to their neurotrophic actions, neurotrophins, particularly, nerve growth factor, mediate various immune and inflammatory responses. These functions are fulfilled by alterations in cytokine and neuropeptide production, through effects on neurotrophin receptor-bearing immune cells, notably, mast cells, lymphocytes, and macrophages. Within skin, different neurotrophins are synthesize and release primarily by keratinocytes, thus affecting cutaneous innervation, postinjury neural reconstruction, and nonneuronal cells, such as melanocytes, through a paracrine action. Involvement of neurotrophins and their receptors in the pathogenesis of certain skin diseases is also reviewed. ***Biomed Rev 1999; 10:15-23.***

THE NOBEL PRIZE

In October 19 8 6, the Nobel Assembly at the Karolinska Institute in Stockholm announced that the 1986 year's Nobel Prize in Physiology or Medicine is awarded to Rita Levi-Montalcini, Rome, Italy and Stanley Cohen, Nashville, Tennessee, USA. The achievements thus awarded are of fundamental importance for the understanding of how cell growth and survival is driven. The general pattern for this process has been known for a number of years, but the regulatory mechanisms behind it was at the time unknown. Thus the discovery of the first neurotrophic factor, nerve growth factor (NGF), by Rita Levi-Montalcini and of epidermal growth factor (EGF) by Stanley Cohen has opened up a completely new and rapidly growing field of research of great, basic and clinical, importance and interest. As a spin-off effect, we now witness an improved understanding of the pathobiology of various diseases, such as neurodegenerative diseases, autoimmune diseases, skin wounds, and cancers. Today, EGF, an "epitheliotrophin", also for skin keratinocytes, is used for *in vitro* growth of these cells under laboratory conditions. This will revolutionize the treatment in severe burn wounds where the lack of suitable skin transplants is critical for the treatment outcome. One cm^2 of skin from the patient can now, with these new biotechnologies, be grown into enough numbers of cutaneous cells to enable the coverage of one m^2 of injured skin. And this new skin will not be rejected, since it originally comes from the patient himself/herself.

For many years scientists around the world were highly fascinated and intrigued by the newly discovered neurons, their axons and dendrites, as well as the synaptic contacts they established. The neurons were found to be very specialized and

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differentiated to be able to cope with the various tasks that we nowadays understand are based within the nervous system. What governs this differentiation process and forms the basis for this amazing network of information channels? How can all the nerve terminals find their way to the right target cell, and how can their synapses be correctly formed and placed?

The history around the answers to these questions began in 1947 when a 38-year old Italian developmental biologist, Rita Levi-Montalcini, joined Viktor Hamburger at the Washington University in St Louis, Missouri, USA. Hamburger, a German scientist and one of the embry ologist Hans Spemann' s foremost pupils, had come to the US A15 years earlier. The scientific work Hamburger had started in his homeland, and continued in the USA. He was at the time appreciated as the greatest in the field of experimental neuroembryology.

Rita Levi-Montalcini was not either untouched by the events before and during the Second World War. In 1936, she had obtained her MD in Turin, and initiated her specialist training in neurology and psychiatry, when Benito Mussolini in June 1938 struck with his racial laws against nonarians. As Italian with a Jewish background, Levi-Montalcini very soon found out that all possible ways of progress and carrier were closed for her. She was not even allowed to borrow books at the university library. She accepted an invitation from the Institute of Neurology in Brussels, but already after less than two years she had to return to Turin to avoid the coming German invasion of B elgium. There was at the moment not any safe place for her at all in Europe, and the alternative was to leave for the USA. However, Rita Levi-Montalcini decided to stay in Turin with her family, and something happened, which clearly shows what kind of scientist she was. And continued to be! Since she was locked out from the university campus, she built her own neuroembryological laboratory in her bedroom in the apartment she rented in Turin. The equipment consisted only of an incubator for cell and tissue culture, an ordinary lamp, a stereomicroscope, a microtome to cut thin tissue slices with, and a set of instruments she had produced herself from sewing needles. Her "bible" at the time was Viktor Hamburger's paper, entitled "The effects of wing bud extirpation on the development of the central nervous system in chick embryos", published in *Journal of Experimental Zoology* 1934; 68:449-494. Ather laboratory, RitaLevi-Montalcini was assisted by her previous teacher, the eminent neuroanatomist GiuseppeLevi, also of Jewish origin. It is from his laboratory that several of the Italian Nobel Laureates have come: Salvador Luria(1969), RenatoDulbecco (1975), and Rita Levi-Montalcini (1986).

Then Turin is attacked, the family escapes to the countryside, where Rita Levi-Montalcini tries hard to keep her research going. The war is constantly coming closer, Mussolini is removed from office, the Nazis are literally flooding Italy, and the battue of Jews takes a horrible start. The family of Levi-Montalcini took flight to Florence, where they had to live in hiding using false identification papers until the end of the war inMay!945.

In 1946, Viktor Hamburger, intrigued by the article by Levi-Montalcini and Levi on the role of neuron-target interactions during development, published in 1942, invited Levi-Montalcini tojoinhiminStLouis.She accepted andby 1947 they had begun experiments that resulted in their first joint article, entitled "Proliferation, differentiation and degeneration in the spinal ganglia of the chick embryo under normal and experimental conditions", published in *Journal of Experimental Zoology* 1949; 111: 457-502. Hamburger suggests that she shall more closely examine some results that one of his previous scholars, Elmer Bueker, have got when he transplanted a mouse tumor to a chicken embryo. Bueker wanted to observe how a quickly growing tissue was furnished with nerve fibers. He received his answer, but overlooked certain other, even more astounding aspects. RitaLevi-Montalcini did not. Indeed, in collaboration with Hamburger, sherepeatedBueker'sexperiments. "Wedid not only find that the growth of sensory ganglia from the embryo to the tumor (sarcoma 180) increased, but also that the sympathetic ganglia increased their volume enormously. They became 5-6 times larger than in the control animals", RitaLevi-Montalcini reported. The neighbouring motor neurons, however, decreased their number. How should this be interpreted? "It was an early day in the Spring of 1951, as "the stone was rolled away from the entrance" and it struck me that the effect of the tumor differed from ordinary embryological tissue; the tumor must secrete some kind of growth factor of unknown chemical identity." When she compared the effects on her experimental animals with those found in untreated controls, she found very obvious and clear differences. At a time-point, when the outgrowth of sympathetic nerve fibers in the control animals not even had started, it was at full speed in the abdominal organs of the chicken embryos. This evident activity, which was proposed to be governed by a diffusible factor derived from the transplanted mouse tumor, even went so far that the nerve fibers invaded the blood vessels of the embryo. That these phenomena were caused by a factor spread *via* the blood, was decisively proven by Rita Levi-Montalcini in anew experiment. She transplanted fragments of the mouse tumor outside of the membrane (chorio-allantois), which enwraps 4-6 days old chicken embryos. Thus, the tumor and the embryo were both supported by the same blood supply, but had no direct contact with each other. The results of this experiment were identical with the ones received when transplanting the tumor tissue directly inside of the embryo" To enable the identification of this unknown factor, Rita Levi-Montalcini utilized tissue cultures. A scholarship from the Rockefeller Foundation gave her the opportunity to realize these experiments at the world famous parasitologist Carlos Chagas' laboratory at the University in Rio de Janeiro. With two mice in her luggage, both with sarcomas transplanted to them, RitaLevi-Montalcini came to Rio de Janeiro. The first experiments failed, but she persistently continued to try to transplant tumor tissue to chicken embryos, followed by dissection of

small tumor fragment, which she placed in the direct vicinity of sensory or sympathetic ganglia in the test tube. "Twenty years later I still recall vividly the astonishment I felt when examining the results in the microscope", she said in 1975. "I had no camera, and did not have time to find one, so, instead, I draw what I saw in black ink. Within 12 hours, the nerve fibers had grown radially from the sensory and sympathetic ganglia in the close proximity to the tumor. It looked like rays from the sun!" Soon this phenomenon became known as the NGF halo. This halo is the most sensitive and reliable sign that this growth factor actually is present in a certain tissue or body fluid, or not (1). Three months after the discovery, Rita Levi-Montalcini returned with her halo effect to Hamburger in St Louis, full of enthusiasm and totally convinced that the remaining work, to identify and characterize the molecule behind this tumor-derived growth factor, only should be a matter of a few months' work. The reality turned out completely different. It should actually take more than 20 years to solve all the chemical issues around this factor, and much of this achievement was enabled due to a very skilled biochemist, namely Stanley Cohen. Stanley Cohen was at the time specialist regarding urea from earthworms. He had actually collected several tons (!) of these animals outside of Denver, Colorado. Luckily, he right then worked at the Washington University in St Louis, heard about the peculiar halo effect, and decided to join the research unit of Hamburger and Levi-Montalcini. In an extract from the mouse sarcoma, Cohen found the active substance within small cytoplasmic particles. In 1954, the growth factor was named nerve growth-stimulating factor, later shortened to nerve growth factor, and hence abbreviated as NGF. The fraction contained both proteins and nucleic acids. It was now up to the scientists to find out in what molecular category that NGF was to be found. "If we digest the nucleic acids in the active fraction and this leads to the disappearance of the growth-promoting effect, we can suspect that NGF is connected to the nucleic acids", they said. "However, if the effect still remains intact after the removal of the nucleic acids, we instead ought to find NGF in the protein pool." Stanley Cohen now followed the advice given by the colleague Arthur Kornberg, at the Stanford University in San Francisco, Nobel Laureate in Physiology or Medicine in 1959 together with Severo Ochoafor the discovery of the mechanism behind the biological synthesis of RNA and DNA. The piece of advice was that he should use snake venom to digest the nucleic acids, since certain snake venoms contain a special enzyme, phosphodiesterase, which will destroy the nucleic acids. Cohen did exactly this. However, now something happened that first was regarded as a complete failure, but turned out to be one of the really lucky event. The history of science is filled with such coincidences. Rita Levi-Montalcini herself said "that it was as to find a hiding place for treasures!" One early Spring morning in 1956, when the scientists as usual inspected the tissue cultures, which had been prepared the day before, they found that the snake venom had amplified the NGF effect in amost astounding way. The normally tender halo of nerve fibers had been transformed into a large halo with a tremendously thick fiber growth. This meant that either the snake venom had destroyed an inhibitory factor in the tumor fraction or actually itself contained NGF. Six hours later they had the answer: if they put diluted snake venom alone to the culture medium, the effect on the sensory and sympathetic nerve cells was the same as if they treated the NGF-containing tumor fraction with the snake venom. The snake venom therefore contained NGF, in a concentration approximately 1000 times higher than in the mouse tumor. Suddenly, Cohen had in his hands a source of NGF which allowed full scale biochemical characterizations, and soon he found that the snake venom NGF is a protein molecule. With this result, Cohen and Levi-Montalcini, as well as other research groups in the world, soon could characterize the same, or similar, NGF from other tissues and body fluids. The big surprise, though, for Cohen and Levi-Montalcini was the finding of NGF in the male mouse submaxillary glands. The tubular cellsofthese glands produce NGF as an oligomeric macromolecule (7S NGF) that is 10 times more active, on a molar basis, than the one in snake venom, and 10 000 times more active than tumor-derived NGF.

In 1971,20 years after RitaLevi-Montalcini's discovery of the nerve growth-stimulating factor, Angeletti and Bradshaw identified the amino acid sequence of beta subunit of NGF (beta-NGF, also known as 2.5S NGF) purified from mouse submaxillary gland. In its active form, NGF is a homodimer, each chain with molecular weight of 13 250 D, and containing 118 amino acids, connected through three disulphide bridges. Subsequently, in 1983, Korsching and Thoenen developed a sensitive two-site immunoassay, allowing the detection of NGF in target organs. With this method it became possible to demonstrate a strong correlation between the density of sympathetic innervation and target levels of NGF, a finding consistent with the neurotrophic theory. Indeed, today the validity of the neurotrophic theory for understanding life and death at neuronal level stands as a crowning achievement of more than 60 years of pursuit by countless investigators.

THE NEUROTROPHINS AMD THEIR RECEPTORS

The known members of the NGF gene family, named neurotrophins, includes NGF, neurotrophin 3 (NT-3), NT-4/5, NT-6, and brain-derived neurotrophic factor (BDNF). The neurotrophin receptors (NTRs) have been named according to the binding constant, as low- and high- affinity receptors. The low-affinity receptor, p75NGF receptor (p75NGFR, also abbreviated as p75 LNGFR, or $p75^{NTR}$) is a member of the tumor necrosis factor (TNF) receptor family (2). This receptor binds all known neurotrophins with similar affinity. The high-affinity NTRs are members of the tyrosine kinase (Trk) receptor family, which includes (*/*) TrkA (gp 140), preferentially binding NGF, *(ii)* TrkB (gp!45),preferentially binding BDNF and NT-4/5, and(m)TrkC (gp!45),bindingsolely NT-3 (2-4). The presence of p75NGFR,

a coreceptor of Trk, increases the affinity of TrkA for NGF, and hence enhances the sensitivity of TrkA-mediated neuronal response to NGF (4,5). On the other hand, NGF can enhance the NGFR expression (6). By targeted mutation of p75NGFR in mouse embryonic stem cells, a markedly decreased sensory innervation by calcitonin gene-related peptide (CGRP) and substance P (SP) immunoreactive nerves was found, accompanied by loss of heat sensitivity and by development of ulcers in the distal extremities (7). Nonetheless, without p75NGFR, Trk receptors are still capable of mediating many important functions (8), while p75NGFR may be involved either in independent signaling leading to programmed cell death (9) or in NGF-p75-ceramide signaling pathway promoting outgrowth of neurons (10). In addition, neurotrophic molecules that do not belong to the neurotrophin family have also been identified. Examples include glial cell line-derived neurotrophic factor (GDNF) (11), ciliary neurotrophic factor (CNTF) (12), and insulin-like growth factors (IGFs), transforming growth factors (TGFs), and fibroblast growth factors (FGFs) (13,14).

THE SKIM

The skin consists of epidermis, dermis, and hypodermis. The epidermis is a continually renewing, stratified squamous epithelium that keratinizes and gives rise to nails and also pilosebaceous apparatus and sweat glands. The epidermis thickness is approximately 0.4 to 1.5 mm, whereas whole thickness of the skin is 1.5 to 4 mm. The dermis is composed of densely-packed collagen fibers, and fibroblasts dispersed among them, whereas the hypodermis is composed of subcutaneous white adipose tissue. The skin impedes the penetration of microorganisms, absorbs and blocks radiation, and inhibits the loss of water. It contains several types of sensory receptors, is involved in temperature regulation, and functions in immunologic surveillance. Each function associates with a specific region of the skin, with a specific cell type, and/or with a specific cellular organelle.

THE NEUROTROPHINS AMD THEIR RECEPTORS IM THE SKIN

Neurotrophins not only are involved in neuronal differentiation and survival, but also exert specific actions on nonneuronal tissues, including in the skin. NGF transcripts have been identified in normal human keratinocytes in primary and secondary cultures, and expression of $mRNA^{NGF}$ was strongly downregulated by corticosteroids (15,16). The keratinocyte-derived NGF is secreted in a biologically active form as assessed by neurite induction in sensory neurons obtained from chick embryo dorsal root ganglia (15). Normal human keratinocytes in culture express low- and high-affinity NGFR, and NGF significantly stimulates the proliferation of normal human keratinocytes in culture, in a dose-dependent manner (16). Intriguingly, normal mouse epidermal keratinocytes *in situ* are targets for B DNF, *NT-3,* and NT-4, and hence these neurotrophins can also act as "epitheliotrophins", controling epidermalhomeostasis(16a). In human skin, at light microscopic level, p75NGFR immunoreactivity has been localized in cutaneous nerves as well as in certain basal keratinocytes (17), and in Meissner and Pacinian corpuscles of the human digital skin (18). At ultrastructural level, p75NGFR immunoreacti vity has been found in the rat lower lip and in primary and permanent canine tooth pulps of the cat (19,20). Ourrecentresults have revealed that p75NGFRis mainly associated with both Schwann cell membranes and perineurium cell membranes in human cutaneous nerve fibers, whereas a minute p75NGFR immunoreacti vity wasfoundin axonalmembranes(21).

As indicated above, neurotrophins and NTRs are crucially involved in the normal development of the peripheral nervous system (22-24), including cutaneous nerves (25-28). Mice overexpressing NGF in the skin have double the normal number of cutaneous sensory neurons, have an increased innervation of the skin and spinal cord, and are hyperalgesic (25-27), whereas those overexpressing BDNF showed notable enhancement of hair follicle innervation, larger Meissner corpuscle sensory endings, and increased number of Merkel cells (28). Using adye-labeled plasma extravasation technique in rats, the extent of transmedian reinnervation of the skin by C-fibers in the inferior alveolar nerve was observed, suggesting that NGF is essential for the development of collateral reinnervation from cutaneous C-fibers (29). Likewise, $mRNA^{NGF}$ expression in denervated adult rat skin can increase 5-10 fold over normal levels in innervated skin, evoking an NGF-dependent collateral sprouting from neighbouring intact sensory axons (30). Altogether, these findings strongly suggest a pivotal role played by NGF in cutaneous nerve reconstruction. Moreover, NGF can also affect nonneuronal cells in the skin. For instance, NGF modulates keratinocyte proliferation in murine skin organ cultures of hair follicles from telogen skin, but not anagen skin. This is associated with a significant mast cell degranulation, indicating hair cycle-dependent effects of NGF on keratinocyte proliferation *in situ,* which may require the presence of mast cells (31). The expression of NT-3 and its TrkC receptor in the skin of C57/BL6 mice is strikingly hair cycle-dependent, with maximal transcript and protein expression seen during spontaneous hair follicle regression (that is, catagen). These findings suggest that the hair follicle is both a source of and target for NT-3 and that NT-3-TrkC signaling is functionally important in controling hair follicle regression (32). Another neurotrophin, NT-4, is required for the survival of a receptor subclass of down-hair follicle nerves that innervate a subpopulation of hair follicles (33). Furthermore, it is believed that the innervation of epidermis, upper dermis, and the upper portion of hair follicles is regulated by a competitive balance between promoting and suppressing effects of various neurotrophins in the mystacial pad of mice (34). In the epidermis, other cell types, along with keratinocytes, express neurotrophins and NTRs. During fetal development,

Merkel cells express p75NGFR and descend into the dermis to meet the nerve fibers extending from the subcutaneous trunk, and branching to form the subepidermal nerve plexus. The expression of NGFR on dermal Merkel cells precedes their connection with immunoreactive small nerves (35). Cultured human epidermal melanocytes also express p75NGFR and TrkC receptor, and hence keratinocyte- and/or fibroblast-derived NGF and NT-3 may modulate melanocyte gene expression (36,37). In addition, exposure to an NGF gradient is chemotactic for epidermal melanocytes and enhances their dendricity, suggesting a paracrine role for NGF in human epidermis (36).

THE NEUROTROPHINS AND THEIR RECEPTORS MEDIATE IMMUNE FUNCTIONS AND ARE INVOLVED IN NEUROGENIC INFLAMMATION

Increasing evidence demonstrates that neurotrophins and NTRs play an important role in both immune responses and neurogenic inflammation. Forinstance,TrkB and TrkC receptors were found in dendritic cells andmacrophages of tonsilar tissue (38), TrkA was expressed in intestine epithelial cells (3 8) and human lymphocytes (39), and TrkB in thymic macrophages (40). In addition, it was found that human T-lymphocytes secrete and respond to NGF *via* TrkA receptor (41). Indeed, NTR expression is widespread in the immune system and other nonneuronal tissues'in the rat (42). In response to various stimuli, NGF, for example, enhances histamine release from and modulate lipid mediator formation by Trk-bearing basophils (43,44), and activates macrophages (45). Similarly, eosinophils produce and respond to NGF and, for instance, NGF induces a selective release of proinflammatory mediators, and promotes survival and cytotoxicity of human eosinophils (46,47). Further, in NGF transgenic mice, an increased number in sympathetic nerves in lymph nodes is found (48), while in inflamed tissues, NGF contributes to the progressive tactile hyperalgesia elicited by repeated touch stimulation (49). In rat experiments, NGF can restore neurogenic microvascular responses towards normal (50). Local injection of NGF can induce thermal hyperalgesia, mediated by the induction of a myeloperoxidase-leucotactic action, followed by a series of events resulting in the hyperalgesia (51). In rats, experimentally-induced sciatic nerve injury leads to an enhanced NGF-mediated hyperalgesia that is reduced by NGF antiserum (52). GDNF and NT-3 can activate the immune system in allogenic graft combinations (53). By intracerebro ventricular or intravenous injection of high amounts of NGF in the rat, phytohaemagglotinin-induced splenocyte proliferation was significantly enhanced, while it was completely prevented by intracerebro ventricular pretreatment with anti-NGF antibodies (54). Inversely, NGF has been shown to inhibit certain immune responses, for instance, BL-4-induced IgE production. This inhibition was not mediated through blocking of CD23 induction nor through IL-4 receptor expression inhibition (55). By NGF administered *invivo,* a significant dose-dependent suppression of lymphocyte proliferation was also observed (56). Since certain neuropeptides are implicated in cutaneous neurogenic inflammation, mostprobably, NGFcould mediate these effects, at least in part, through stimulation of local neuropeptide synthesis and/or release (cf. Ref. 57). Experimental inflammation, produced by Freund's complete adjuvant, results in a local sensory hypersensitivity, an up-regulation of the SP and CGRP synthesis in the inflamed tissue, and an elevation of NGF levels in the skin. Prior systemic administration of anti-NGF antibodies prevents the behavioral sensitivity, the upregulation of neuropeptide production, and the inflammation-induced expression of immediate early *c-fos* gene in dorsal horn neurons, without modifying swelling and erythema (5 8; also see 59). NGF also stimulates CGRP synthesis in primary afferent neurons without causing long-lasting changes in thermal nociceptive thresholds (60), whereas locally administered NGF increases CGRP expression in dorsal root ganglion neurons (61). Likewise, NGF can completely recover both CGRP and SP content, and still function in capsaicin-impaired sensory neurons (62). Evidence is also reported that NGF regulates cutaneous C-fiber heat nociceptors in the developing rat (63) and that BDNF regulates somatostatin and neuropeptide tyrosine (NPY) expression (64). However, in injured rat lumbar dorsal root ganglion neurons, NGF downregulates both CGRP and SP but not somatostatin expression (65). Finally, NGF has also been demonstrated to stimulate NPY production in human lymphocytes (66).

THE NEUROTROPHINS AND THEIR RECEPTORS IN SKIN DISEASES

Rapidly accumulating evidence implicates neurotrophins and NTRs, through their effects on multiple immune functions and on neurogenic inflammation, in thepathogenesis of numerous diseases affecting the skin. In psoriatic skin, for example, an increased NGF expression has been observed, and an increased number in nerve terminals was associated with increased SP and CGRP levels, suggesting that NGF may directly, or through neuropeptide release, be involved in the development of psoriasis (67). Furthermore, NGF may increase the mitogenic potetial of IGF-1, IGF-2, TGF-p\ and basic FGF in human keratinocyte cultures (68). In prurigo nodularis skin, an increased p75NGFR expression in dermal nerves has been documented (69). Overexpression of p75NGFR was mainly found in Schwann cell membranes and perineurium cell membranes, accompanied by an increased CGRP expression (70) and by p75NGFR immunoreactive nerve association with mast cells (71). It is note worthy that mast cells are source of and target for NGF, and, accordingly, an interactive involvement of NGF and mast cells in the pathogenesis of various diseases is increasingly recognized (reviewed in 72,73). Likewise, NGF is reported to induce inhibition of TNF-oc production, implying an antiin-

flammatory role of NGF, through effects on mast cells (74). Furthermore, NT-3 is shown to be increased in the skin of human diabetic neuropathy (75), whereas TrkA and TrkC expression increased in human diabetic skin (76). Moreover, NGF, by upregulating *bcl-2* expression, rescues melanocytes from ultraviolet-induced apoptosis, suggesting that keratinocyte-derived NGF may be protective to melanocytes (77). Likewise, experimental skin wound is accompanied by an increased expression of NGF (78,79), whereas topically applied NGF accelerates the healing rate in normal and healing-impaired diabetic mice (78). These findings suggest that the endogenous NGF secretion is insufficient for complete restoration of skin integrity in wound healing, and hence exogenous administration of NGF is required to benefit the healing process. Importantly, this is also thecase with human ulcers: topical treatment with NGF promotes the healing of corneal (80) and skin (81) ulcers.

CONCLUSION AMD PERSPECTIVES

Evidence presented here shows that neurotrophins and their receptors play an important role in the skin development and function as well as in the pathogenesis of certain skin diseases. Also, neurotrophins, in particular NGF, have no longerpredominantly been considered under the aspect of their function in regulating neuronal differentiation and survival. Instead, these molecules are well recognized to have a number of potent effects on various nonneuronal cells, including immune cells. The development of NGFR and Trk receptor agonists and antagonists, as well as enhancers and inhibitors of neurotrophin synthesis (82, this volume of *Biomedical Reviews),* will likely lead to a breakthrough in the treatment of certain skin diseases.

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