We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

13

Melanoma and the Nervous System – Novel Pathways Mediated by Neurotrophins and Their Receptors

Carlo Pincelli, Katiuscia Dallaglio and Francesca Truzzi
Institute of Dermatology, School of Biosciences and Biotechnologies, University of Modena and Reggio Emilia, Modena
Italy

1. Introduction

Human melanoma is the deadliest form of skin cancer in the world, and its incidence is rapidly increasing every year 3-7% on average of the last decades, pointing to melanoma as one of the biggest health problem worldwide (Perlis & Herlyn, 2004). Recent statistics show that melanoma represents 1-3% of all malignant tumors, with Australia and New Zealand having the highest incidence (40 new cases/100 000 inhabitants per year), followed by North European countries and the USA; on the other hand, Japan and central Africa share the lowest incidence. Melanoma is one of the most aggressive tumors. Up to one-fifth of patients progress to metastatic (stage IV) disease, with a median survival of 6 months and a 5-year survival rate of less than 5% (Balch et al., 2001). Melanoma is resistant to conventional therapy such as chemotherapy, radiotherapy and immuno-therapy, as only 5-20% of the patients show a positive response to these treatments. To date, the only FDA-approved chemotherapy for melanoma is the alkylating agent dacarbazine (DTIC), which gives clinical responses in 5–10% of patients and cures in about 1%. The only other approved agents for disseminated melanoma are interleukin (IL)-2 and interferon (IFN)-a, which also have low response rates. During the radial phase, melanoma cells spread horizontally, while during the vertical phase they are able to invade the dermis and become able to generate metastasis (Garbe et al., 2011). Usually, the two phases represent the step-process that leads to aggressive melanomas: once melanoma has spread beyond its original location, it is usually highly resistant to therapies. There are four major types of melanoma: superficial melanoma, the most common type, flat and irregular in shape and colour, nodular melanoma, lentigo maligna melanoma, usually occuring in the elderly, and finally, acral lentiginous melanoma, the least common form of melanoma, which develops at high incidence in African Americans. Melanomas may develop in or near a previously existing precursor lesion or in healthy skin, and they can appear in the mouth, eye, or retina at the back of the eye, vagina, esophagus, anus, urinary tract, and small intestine. Age, sunburns during childhood, close relatives with a history of melanoma, presence of displastyc moles, weak immune-system, long-term exposure to sunlight and exposure to carcinogens are the most common risk factors for melanoma development. Melanoma originates from mutated melanocytes, which share with neurons a common neuroectodermal origin. Among the molecules that act as

neurotrophic factors, neurotrophins (NTs) and their receptors constitute an important network.

2. Neurotrophins

NTs are a family of structurally and functionally related proteins, initially identified as promoters for neuronal survival. During a search for survival factors, nerve growth factor (NGF) was initially identified (Levi-Montalcini, 1987). Secondly, brain-derived neurotrophic factor (BDNF) was characterized as a survival factor for several neuronal populations not responsive to NGF (Barde et al., 1982). These two proteins revealed conserved features of the sequences, leading to isolation of clones encoding additional members of this family. NT expressed in mammals are four: NGF, BDNF, neurotrophin-3 (NT-3) and NT-4. NTs play a critical role in developmental neurobiology; they are crucial in cellular interactions, in regulating synapse formation and plasticity (Huang et al., 2003), in controlling cell survival and differentiation (Segal, 2003). NTs effects are mediated by two classes of cell-surface receptors, a family of tyrosine kinase receptors called Trks (TrkA, TrkB and TrkC) and the p75 neurotrophin receptor (p75NTR). Trk receptors bind NTs with higher affinity and specificity. In particular, TrkA binds NGF and NT-3, TrkB binds BDNF, NT-3, NT-4/5. TrkC only binds NT-3. On the other hand, p75NTR binds all NTs with low affinity and specificity.

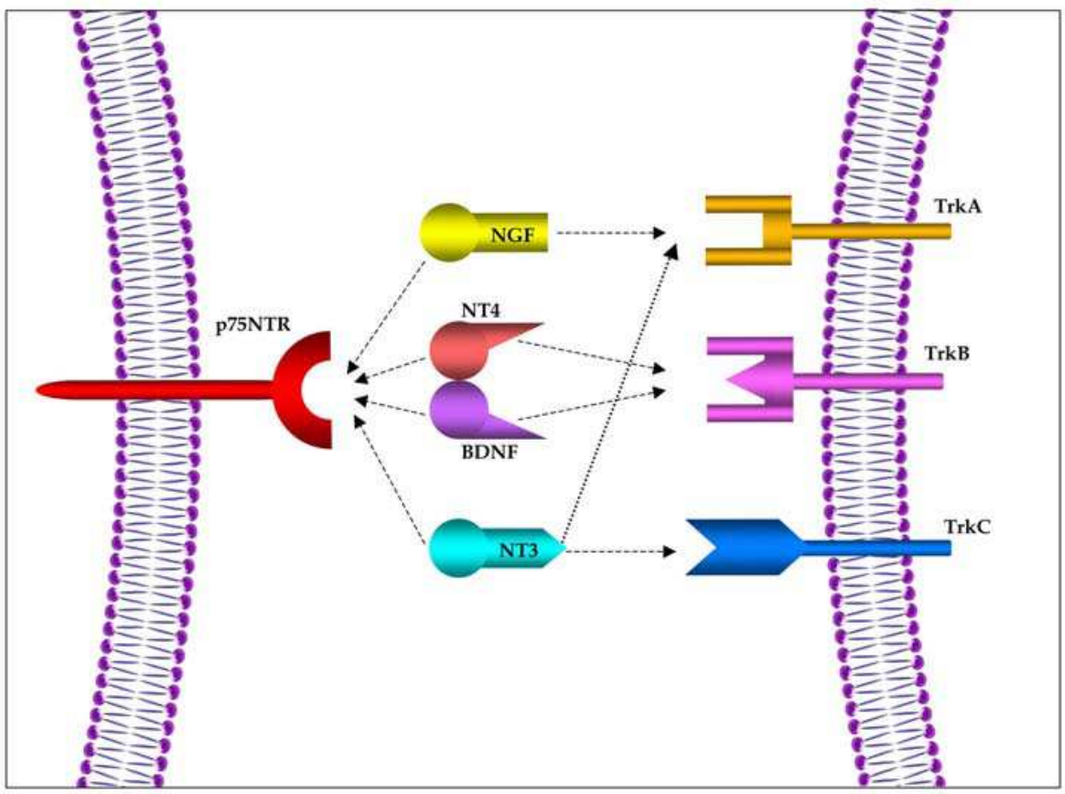


Fig. 1. NTs and their receptors

Trks are tyrosine kinase receptors with similar structure. They are activated by ligand-induced formation of noncovalently associated receptor dimers. In addition to the three full-

length Trk proteins, all three trk genes encode other protein isoforms by alternative splicing in the extracellular and intracellular domains, which include insertions in the extracellular domain (Barker et al., 1993; Tacconelli et al., 2005) and deletions or added residues in the intracytoplasmic domain (Reichardt, 2006). Several different mutation types in the trkA gene have been identified in congenital insensitivity to pain with anhydrosis (CIPA) patients (Indo, 2001). The phenotypes associated with CIPA are believed to result in large part from loss of NGF-dependent neurons, including nociceptive sensory and sympathetic neurons, during embryogenesis. A dominant mutation in TrkB (Y722C) that impairs TrkB kinase signalling has recently been described in a patient with severe hyperphagic obesity and severe impairments in nociception, learning and memory (Yeo et al., 2004).

The biological effects induced by NTs strongly depend on the pattern of NT receptor/co-receptors expression in target cells as well as onset of intracellular adaptor molecules that link NT signaling to different biochemical pathways. The propensity of NTs to produce diametrically opposing effects on cell survival has led to propose a "yin and yang" model of neurotrophin action, where the binary actions of NTs depend on both the form of the neurotrophin (pro- versus mature) and the class of receptor that is activated (Lu et al., 2005). Central to the proposed "yin–yang" model of NTs function is the observation that a mature NT binds preferentially to Trk receptors to enhance cell survival, whereas an unprocessed proNT binds to p75NTR to induce cell death. NTs interaction with Trks require receptor dimerization, autophosphorylation, and the subsequent binding of adaptor molecules that couple Trk receptors to different intracellular signal transduction pathways (Reichardt, 2006). NTs interact with trks receptors at the membrane-proximal immunoglobulin-like domain. The three-dimensional structures of this domain in each of the Trk receptors have been solved (Ultsch et al., 1999). Expression of a specific Trk receptor confers responsiveness to the NT to which it binds. On the other hand the isoform of TrkA including an insert is also activated by NT-3 in addition to NGF (Clary & Reichardt, 1994), while the similar isoform of TrkB is activated by NT-3 and NT-4 in addition to BDNF (Strohmaier, 1996). 36 novel isoforms of TrkB proteins with unique properties have been described recently. This suggests high complexity in the synthesis, regulation and function of this important NTs receptor, emphasizing the need for further study of these novel TrkB variants (Luberg et al., 2010). TrkC has several characteristics of a tumor suppressor: its expression in tumors has often been associated with good prognosis. It was recently demonstrated to be a dependence receptor, transducing different positive signals in the presence of ligand but inducing apoptosis in the absence of ligand. (Tauszig-Delamasure et al., 2007). Differential splicing of trkC mRNA also results in expression of a TrkC isoform with an amino acid insert within the tyrosine kinase domain. This insert appears to modify the substrate specificity of this tyrosine kinase, inhibiting activation of several substrates and interfering with its ability to promote neuronal differentiation (Guiton et al. 1995).

p75NTR was the first NT receptor to be identified as a low-affinity receptor for NGF, but it was subsequently shown to bind each of the neurotrophins with a similar affinity (Rodriguez-Tébar et al., 1990; Frade & Barde, 1998). p75NTR belongs to the tumor necrosis factor receptor superfamily. It has an extra-cellular domain containing four cysteine-rich motifs, a single transmembrane domain and a cytoplasmic domain that includes a 'death' domain, similar to those present in other members of this family (He & Garcia, 2004). This receptor does not contain a catalytic motif, however it interacts with proteins that transmit crucial signals for regulating neuronal survival and differentiation as well as synaptic plasticity. The three-dimensional structure of the extracellular domain of p75NTR in

association with an NGF dimer indicates that each of the four cysteine-rich repeats participates in binding to NGF (He & Garcia, 2004). The binding of NGF to p75NTR may result in dissociation of p75NTR multimers and is compatible with the possibility that Trk and p75NTR monomers simultaneously bind the same NT dimer. A gene related to p75NTR, named NRH-2, has recently been identified. The product of this gene lacks the extracellular cysteine-rich repeats present in p75NTR and fails to bind NGF, but it is able to interact and influence the ligand-binding properties of TrkA (Murray et al., 2004). When p75NTR is expressed alone, mature NTs are capable of inducing apoptosis or promote survival depending on the intracellular adaptor molecules present in target cells by interacting with a mounting number of downstream molecules (Wang et al., 2000). However, signaling through p75NTR may also promote cell survival acting through the NF-κB pathway (Roux & Barker, 2002). The coexpression of Trks and p75NTR increases high affinity NT binding, enhances Trk ability to discriminate a preferred ligand from the other NT, and promotes NT survival effects (Teng & Hempstead, 2004). On the other hand, the proform of NT, proNGF, binds p75NTR in association with its co-receptor sortilin, but not Trk (Nykjaer et al., 2004). More specifically, sortilin, a member of the vps-10 protein family, binds the ''pro'' region of NGF, whereas p75NTR binds mature NGF. The p75NTR–sortilin complex couples with proNGF to induce apoptosis (Kaplan & Miller, 2004).

3. NTs and skin microenviroment

NTs also operate in a number of non-neuronal tissues, including skin where a complex NT network exists with various cells that are either the target or the source of NTs, thus playing autocrine and paracrine functions (Botcharev et al., 2006). Moreover, given the common neuroectodermal origin of the skin with the nervous system, different studies have been carried out on the role of NTs and their receptors in the cutaneous system. First, NGF, which is synthesized in the epidermis, is retrogradelly transported to the ganglia to stimulate the release of neuropeptides in the skin, thus favoring cutaneous neurogenic inflammation (Davis et al., 1997). Moreover, null mutations of genes in the NTs and their receptors lead to loss/reduction of specific neurons in sensory ganglia; conversely, cutaneous overexpression of NTs results in skin hyperinnervation and increase in the number of sensory neurons innervating the skin (Montaño et al., 2010). Not only NGF is neurotrophic at the skin level, but it possesses a number of biological effects also in cutaneous cells. Normal human keratinocytes synthesize and release NGF that can act as a growth factor for these cells (Pincelli et al., 1994). The most common type of skin cells is the keratinocyte. These cells synthesize and secrete all NTs (Di Marco et al., 1991), NGF being secreted at highest levels as compared to the other NT. In human keratinocytes, NT-3 and NGF upregulate each other's secretion. UVB irradiation downregulate NGF, while UVA augment NT-3 release (Marconi et al., 1999; Stefanato et al., 2003). Human keratinocytes release NGF in increasing amounts while proliferating, whereas secretion ends in more differentiated cells (Pincelli et al., 1994). NGF induces human keratinocyte proliferation (Di Marco et al., 1993) and it can either stimulate or inhibit murine epidermal and hair follicle keratinocyte proliferation *in situ (*Paus et.al., 1994). Human keratinocytes express the high affinity receptors TrkA and TrkC, but not the functional form of the TrkB (Marconi et al., 2004). Endogenous NGF autocrinally sustains keratinocyte proliferation. NTs together with their receptors TrkA and TrkB can stimulate proliferation of mouse keratinocyte in *ex-vivo* cultured skin explants (Paus et al., 1994; Botchkarev et al., 1999). Moreover, NTs modulate susceptibility to

apoptosis in the epidermis. Autocrine NGF protects human keratinocytes from UVB-induced apoptosis, while UVB downregulates both NGF and TrkA expression in these cells (Marconi et al., 1999). Because in normal human keratinocytes TrkB lacks functional isoform, NT may exert different functions by binding p75NTR alone. In this context, p75NTR acts as a proapoptotic receptor. This is exemplified by BDNF and NT4, which induce a higher rate of apoptosis in normal human keratinocytes overexpressing p75NTR, as compared to mock-transfected cells. On the other hand, p75NTRsiRNA-transfected keratinocytes fail to undergo cell death after administration of NT4 (Truzzi et al., 2010). Interestingly, stem keratinocytes (KSC) expresses most of the NGF produced by human keratinocytes (Marconi et al., 2004), and inhibition of TrkA reduces the proliferation of this keratinocyte subpopulation (Marconi et al., 2004). This suggests that the presence of a NGF-TrkA autocrine loop, which acts both as mitogenic and as survival factor, contributing to the maintenance of the so-called "stemness" in keratinocytes. Conversely, p75NTR is mostly expressed in the differentiated transit amplifying (TA) cells, and it is barely detected in KSC. TA cells have been shown to be more susceptible than KSC to apoptosis (Tiberio et al., 2002). Therefore, the espression of p75NTR predominantly in TA cells seems to be consistent with the pro-apoptotic role of this receptor in human keratinocytes (Truzzi et al., 2011).

Another important epidermal cell is the melanocyte that localizes in the dermo-epidermal junction and in the hair matrix. NTs are important for melanocyte migration, viability and differentiation together with other paracrine signalling molecules (Pincelli et al., 1997). Normal human melanocytes are a target of the NTs skin network, because they express all the NTs receptors both *in vitro* and *in vivo (*Marconi et al., 2006). Normal human melanocytes also express p75NTR, which is upregulated by different stimuli, like UV irradiation (Peacocke et al., 1988). NTs influence melanocytes in a paracrine fashion. NGF is implicated in melanocyte survival (Zhai et al., 1996), migration and dendricity (Yaar et al., 1991), and its synthesis and secretion are enhanced by UV irradiation (Tron et al., 1990). Moreover, NGF reduces apoptosis when melanocytes are irradiated with UV, through upregulation of the anti-apoptotic Bcl-2 protein *in vivo* (Stefanato et al., 2003). Thus, NTs are important for protection of UV-induced oxidative stress and apoptosis in melanocytes. Melanocytes produce all NTs, while when these factors are added to the cultures, they fail to stimulate cell proliferation (Marconi et al., 2006). When melanocytes are maintained in growth factor-depleted medium, NGF and NT-3 promote melanocyte survival (Yaar et al., 1994). Both NT3 and NT4 secretion promotes the synthesis of tyrosinase and tyrosinase-related peptide (TRP)-1, critical enzyme of melanin biosynthesis (Marconi A et al., 2006). Human melanocytes express Trk receptors (Marconi et al., 2006; Yaar et al., 1994). Interestingly, phorbol 12-tetra decantate 13 acetate (TPA), a strong activator of protein kinase C, induces the expression of TrkA (Yaar et al., 1994) and decreases the expression of TrkC, suggesting that NGF and NT3 mediate different signals through their specific high affinity receptors. Melanocytes express also the NT low affinity receptor p75NTR, which expression is upregulated after TPA treatment (Yaar et al., 1994).

NTs and their receptors are expressed both in dermal fibroblasts and in the more differentiated myofibroblasts. p75NTR and TrkB are expressed at higher levels in myofibroblasts than in fibroblasts, which in contrast express higher levels of TrkA. Dermal fibroblast and myofibroblasts secrete all NTs, modulating dermal fibroblast proliferation. Interestingly, NTs also promote fibroblast differentiation into myofibroblasts, by inducing α-SMA expression. This indicates that NTs could have a functional role in the fibro-myofibroblast system (Palazzo et al., 2011). It has been shown that NGF induces fibroblast-

like keratinocyte differentiation into myofibroblasts (Micera et al., 2001), their contraction in 3D collagen matrix (Micera et al., 2001) and the expression of MMP-9 (Metalloprotease-9) in keratoconjunctivitis-derived fibroblasts (Micera et al., 2007b), and different works show the applicative possibility of this NGF function (Landi et al., 2003; Aloe et al., 2008; Sun et al., 2010). All NTs promote fibroblast migration, while NGF and BDNF promote their contractile activity. Therefore, NGF and BDNF, produced by dermal and epidermal cells, could be key regulators of the biomechanical properties in the dermis.

In the skin network, NT and their receptors are also important for other epidermal cells. Skin mast cells express functional TrkA, produce NGF (Marshall et al., 1999), and express p75NTR (Fischer et al., 2008). Merkel cells are sensory cells of neural crest origin. During development, neither NT-3 nor TrkC and p75NTR are expressed by Merkel cells in the murine whisker. However, NT-3 is essential for mice postnatal survival (Szeder et al., 2003). Moreover, both TrkB and p75NTR were shown to be important for Merkel cell development (Perez-Pinera et al., 2008; Kinkelin et al., 1999).

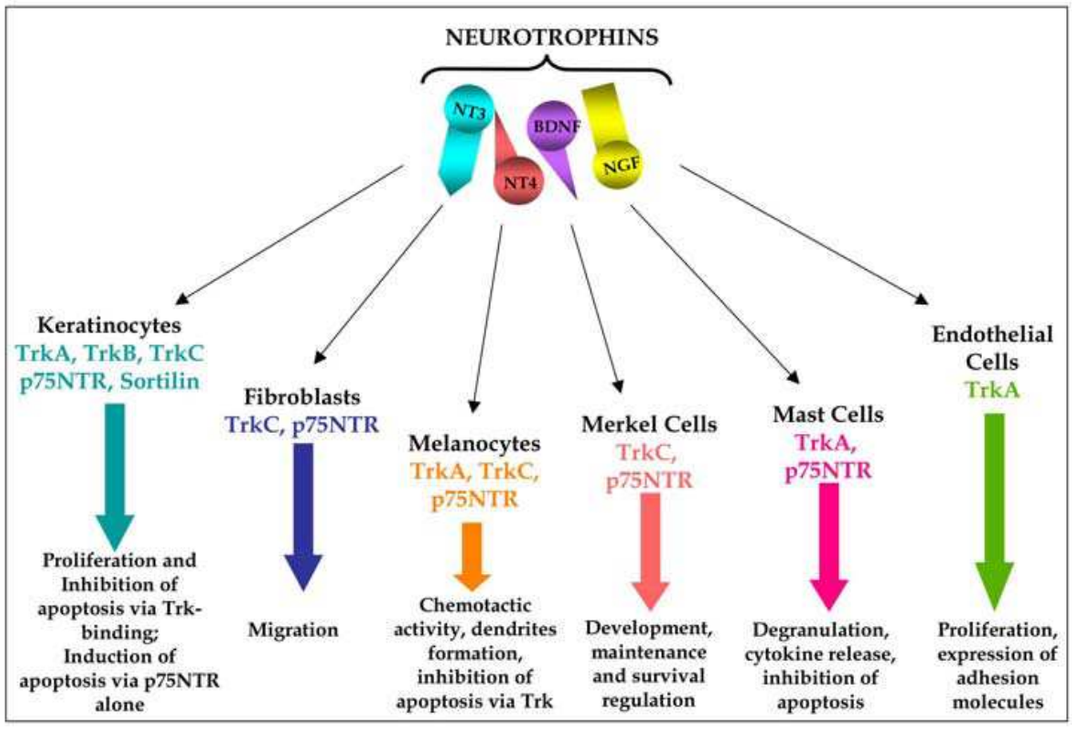


Fig. 2. NTs in the skin network

4. NTs and the origin of melanoma

Melanocytes, the cells that originate melanomas, are melanin-producing cells responsible for skin, hair and eye pigmentation. The principal role of melanocytes is to protect human skin from UVB radiation-induced stress. To understand melanoma origin, it is of paramount importance to elucidate the characteristics of the cells that originate the tumor. Indeed, melanocytes have intrinsic properties such as migratory capacity and self-renewal, which are shared with melanoma cells, and that could be partially responsible for the high

susceptibility of melanoma to metastasize and recur in patients. Human melanocytes derive from a group of embryonic cells that form, during embryogenesis, the neural crest (NC). Neural crest cells (NCC) are multipotent, giving rise to different cell lineages depending on their anatomic location, and are therefore referred to as NC stem cells (NCSC). Melanocytes appear to derive from both cranial and trunk neural crest, while cells derived from the vagal, sacral, mid/hindbrain regions of the crest originate neurons cartilage, bones, smooth muscle, peripheral and enteric neurons and glia (Anderson et al., 2000). These multipotent cells give rise to a bipotent NCSC that generate both glia and melanoblasts (Dupin et al., 2000). Although the mechanism of lineage restriction towards melanoblasts specification has been deeply studied, it is only partially understood. However, it seems that signals from surrounding cells control this mechanism, both during cell homing and in their final environment. The bipotent progenitor is able to generate a melanocyte-restricted cell, which is referred to as melanoblast. Melanoblasts are unpigmented cells that migrate from the neural crest site along the dorsolateral pathway, throughout the developing epidermis. They colonize both interfollicular epidermis, localizing at the basement membrane, and developing hair follicles. In interfollicular epidermis, melanoblasts differentiate into mature melanocytes, upon stimulation from neighbor keratinocytes. In the hair follicle, melanoblast can then further segregate into a committed melanocyte or an adult melanocyte stem cell (Nishikawa & Osawa, 2007). The committed melanocyte resides in the hair matrix of the follicle and differentiates into a melanin-producing cell, thus being responsible for hair pigmentation. As opposite, melanocyte stem cells, which reside in the bulge area of hair follicles, are amelanotic and conserve characteristics of stem cells such as slow-cell cycle/quiescence and self-renewal capacity (Nishimura et al., 2002). The presence of these cells ensures the pigmentation of hair follicles in subsequent hair cycles. In humans, melanocyte stem cells have not been isolated yet (Sabatino et al., 2009). However, in patients affected by vitiligo, a progressive skin disease with defective pigmentation, the repigmentation process starts from perifollicular areas, thus implying that, during this process, undifferentiated melanocytes in interfollicular epidermis may derive from melanocyte stem cells of the hair follicle bulge area (Falabella & Barona 2009). Consistently, a migration process of bulge melanoblasts towards interfollicular epidermis has been previously observed (Cui et al., 1991). Overall, these observations may suggest that melanoblasts in the hair follicles function as a reservoir population both for the bulb hair follicle and for interfollicular epidermis.

Upon UVB radiations and exogenous stress stimuli, melanocytes can acquire genetic mutations. Although apoptosis usually eliminates highly damaged mutated cells, some of these mutations can confer resistance to apoptosis and proliferative advantage to the cells, thus leading to accumulation of mutations and to the formation of melanocytic lesions. The old carcinogenesis model, namely "the stochastic model", suggests that virtually any cell could be the target of mutations and subsequent transformation. As opposite, different works suggest that only some cells retain the susceptibility to acquire mutations and generate cancer, and that these cells can either be differentiated or have stem cells characteristics. Whether melanoma arises from melanocyte stem cells or a differentiated melanocyte is still matter of debate (Hoek & Godin, 2010). It is possible that differentiated melanocytes undergo a process of de-differentiation, thus acquiring stem cell characteristics. Melanocyte stem cells in the hair follicle generate an amplifying progeny, which is differentiated, still retaining self-renewal capacity. After exiting stem cell niche, transit amplifying melanocytes colonize adjacent vacant spaces and repopulate them, thus

functioning as stem cells (Nishimura et al., 2002). In quails, melanocytes removed from their niche and clonally cultured, can generate multipotent cells retaining self-renewal capacity, thus confirming that de-differentiation of melanocytes is indeed possible (Real et al., 2006). It has been proposed that melanoma arises in a stepwise process, starting from nevus and dysplastic nevus stages to in situ melanoma and finally, to metastatic melanoma. Because nevi seems to originate from mutations in a precursor cell, which then activates proliferative pathways, while suppressing apoptosis, it would be more likely that melanoma arises from a mutated cell with stem characteristics. However, this model does not mimic precisely melanoma biology, as melanoma can arise in absence of nevus precursor, and displastyc nevi do not necessarily evolve into melanomas (Beona et al., 2003). In many other systems, stem cells are considered the best candidate for accumulation of mutations, given their long persistence in the tissue and retaining the highest proliferative potential. Although the cell at the origin of melanoma is still unidentified, recent works suggest that melanocyte stem cells located in the hair bulge may not be the right candidate. Indeed, primary melanoma localizes at the junction between dermis and epidermis, suggesting that stem melanocytes should migrate from hair follicles to the epidermis before generating melanomas. Moreover, while epidemiological studies demonstrate a correlation between melanoma formation and UV-radiation-induced sunburn in childhood, hair follicles are only marginally reached by UV, because of their deep localization in the tissue. On the other hand, transgenic mice overexpressing NRAS and β-catenin develop melanocytic lesion in the follicle bulge, thus indicating that melanocyte stem cells in the hair bulge are potentially able to mutate and generate melanocytic lesions (Delmas et al., 2007). Up to now, the exact localization of the melanoma precursor and the differentiation state of this cell are still unclear.

Although NCSC contribution to melanoma formation is still controversial, NCSC migration during embryogenesis and tumor formation are tightly connected. Indeed, extravascular migration process, which guides cells towards their final sites, is shared between melanoma cells and NCSC (Lugassy & Barnhill, 2007). In addition, NCSC behavior is influenced by NTs and their receptors, which in turn are part of melanoma microenvironment. Epidermal-restricted NCSC express all NTs, while NGF and NT-3 support their proliferation as well as survival of daughter cells, in that NGF and NT-3 depletion results in loss of 70% and 60% neurons, respectively (Dasari et al., 2008; Zhang et al., 1997). Moreover, NTs can either support proliferation or induce apoptosis in NCC, depending on their lineage/differentiation stage (Langtimm-Sedlak et al., 1996). Consistently, different expression of trk receptors may identify distinct subpopulations of early NCC. While Trk receptors are not expressed at early stages of embryonic development, p75NTR is the first NT receptor to be expressed in NCC (Rifkin et al., 2000). NCSC have been previously isolated from mouse trunk neural tubes by using a monoclonal antibody against p75NTR. p75NTR-positive cells derived from mouse neural tubes are multipotent and have self renewal capacity, generating multipotent progeny. These cells can differentiate into smooth muscle cells, neurons and glial cells, melanocytes, cartilage and bone. They can also generate clonal subpopulations of cells able to generate only glia and neurons, thus suggesting their ability to generate also committed progenitors (Stemple & Anderson, 1992). p75NTR, also knwon as CD271 (Rogers et al., 2008), was successfully used to isolate multipotent stem cells also from rat sciatic nerves (Morrison et al., 1999). These cells generate neurons and glial cells when injected into chick embryos, and retain self-renewal capacity. Multipotent NCSC can be isolated from hairy skin in humans and mice (Sieber-Blum & Grim, 2004; Sieber-Blum et al., 2004). Consistently, p75NTR-positive cells, isolated from human hair follicle dermal

papillae, retain multipotency and contribute to the renewal of neural and non-neural cells, including melanocytes (Yu et al., 2006). Recently, multipotent cells with NCSC characteristics have been extracted by sphere formation from the dermis of human foreskins lacking hair follicles. These cells, not only express stem cells markers such as Oct-4 and nestin, but display also multipotency and the ability to differentiate into multiple lineages, including melanocytes. Moreover, they express p75NTR, thus suggesting that p75NTR can be considered a good marker for NCSC (Li et al., 2010; Paratore et al., 2001).
Melanoma development is considered a stepwise process in which mature melanocytes in the epidermis progressively acquire genetic mutations in oncogenes or tumor-suppressor genes that lead from benign to dysplastic nevi, progressing toward radial growth phase to vertical growth phase, ultimately followed by metastatic melanoma. Melanomas arise within the epidermis and then invade the basement membrane to eventually disseminate to multiple organs. During progression, melanoma moves from the epidermal to the dermal microenvironment by virtue of various mechanisms that involve different cell types, such as keratinocytes, fibroblasts and a number of cytokines and growth factors. While in human epidermis, a functional symbiosis exists between keratinocytes and melanocytes, melanoma cells are refractory to the regulation by keratinocytes and become independent, by autocrinally producing their growth factors (Crowson et al., 2007). The NTs network involves most skin cell types and is responsible for various activities. (Botchkarev et al., 2006). In particular, melanocytes, which share with neurons a common neuroectodermal origin, express all NTs and their receptors.

5. NTs and melanoma

As for many other growth factors, dysregulation of NT signal transduction is found in a number of tumors inside and outside the nervous system where they accompany or contribute to malignant transformation (Kruttgen et al., 2006). Yet, the precise role of NTs and their receptors has to be clarified (Thiele et al., 2009; Papatsoris et al., 2009). On the other hand, NTs have been widely investigated in neuroblastoma (NB) and medulloblastoma, tumors derived from the neural crest. Trk-receptors have been identified as important prognostic factors, influencing the heterogeneous clinical behavior of NB (Nakagawara, 1993). TrkA and/or TrkC expression is present in favorable NBs, which tend to show a more differentiated neuronal phenotype and highly correlates with patient survival (Nakagawara, 2001; Brodeur, 2009; Yamashiro, 1996). The tendency of NBs to regress may be related to their dependence on an inadequate amount of NGF supplied from stromal cells and a differentiating rather than a proliferative response to this NT. Therefore, an autocrine or paracrine TrkB/BDNF pathway may contribute to an unfavorable outcome in primary NBs. The different clinical implications of the Trk receptors and their isoforms strongly suggest that the activation of full-length and truncated TrkA and TrkB may exert different influences on the biological behavior of NB cells (Barbacid, 1994). Like NB, medulloblastoma can be subdivided in many subtypes with different prognosis (Johnsen et al., 2009). TrkA or TrkC has been detected in such areas, in parallel with concentrations of apoptotic or differentiating cells (Ohta et al., 2006). TrkC has been correlated to positive prognosis in medulloblastoma (Segal et al., 1994) and to apoptosis *in vitro* in primary medulloblastoma (Kim et al.,1999). Nevertheless, the effect of p75NTR on the cellular response to NT is complex and may depend on the concentration of ligand, the ratio of receptors, the cell type in which it is expressed, and its stage of differentiation (Greene et al., 1995; Chao et al.,

1995). Overexpression of p75NTR increases the number of high- and low-affinity NGF binding sites in TrkA- expressing PC12 cells (Hempstead et al., 1992). Moreover, p75NTR induces apoptosis in the presence of NGF (Bunone et al., 1997), but this apoptotic signaling is inhibited by the presence of TrkA receptors (Eggert et al., 2000). Recently, it has been demonstrated that the effects of necdin, a protein known to interact with NTs receptors, on the susceptibility of NB cells to oxidant stress depend on the p75NTR/TrkA ratio in the cell (Ingraham et al., 2011).

Although melanoma is a tumor derived from the neural crest, and shares with cancers of the same origin embryogenic and oncogenic pathways as well as common transcription factors (Wang et al., 2008; Gershon et al., 2005), it has been given less attention, as far as the role of NT. Melanomas can be morphologically subdivided in several subtypes, such as epithelioid, pleomorphic spindle cell and desmoplastic melanoma. Iwamoto et al. found detectable p75NTR in 13 of 14 benign nevi, primarily in the spindled nevocytic structures within the dermis (Iwamoto et al., 2001). Moreover, p75NTR is weakly expressed in the epithelioid melanomas, while it is highly expressed in desmoplastic and spindle cell melanomas (Iwamoto et al., 1996). This was confirmed by others who showed p75NTR staining to be more diffuse and intense as compared with S100 (Kanik et al., 1996; Lazova et al., 2010). On the contrary, Huttenbach and co-workers detected p75NTR positive cells only in 33% of desmoplastic melanomas (Huttenbach et al., 2002). Marchetti et al, by using melanoma cell lines, observed that NGF/p75NTR signaling promotes the survival of melanoma cells (Marchetti et al., 2003). They also observed the presence of NGF and NT-3 in tumor adjacent tissues at the invasive front of melanoma brain metastases, which might indicate a paracrine activation of p75NTR and TrkC in melanoma cells by NGF and NT-3 produced by nearby glial cells. Besides promoting melanoma cell survival, NTs also induce the expression in melanoma cells of heparanase, an important enzyme for local invasion and metastasis, that cleaves heparan sulfate chains of proteoglycans, thus modifying the extracellular matrix of tumor cells (Walch et al., 1999). Moreover, Shonukan et al showed that NTs are chemotactic for melanoma cells, and that the actin-bundling protein fascin co-immunoprecipitates with p75NTR in an NGF-dependent manner (Shonukan et al., 2003). In addition, TrkA is expressed by primary and metastatic melanomas and is associated with poor clinical outcome (Flørenes et al., 2004). Recently, during a functional characterization of human cancer-derived TrkB mutations, one additional TRKB point mutation proximal to the kinase domain (TRKB(P507L)) in a human melanoma cell line was found, even if it was functionally indistinguishable from wild-type TRKB in both *in-vitro* and *in-vivo* (Geiger et al., 2011). As melanoma could originate from melanocytes and melanocytes seem to benefit from the cutaneous neurotrophic network mainly as paracrine targets, once malignant transformation occurs, melanoma cells acquire self-renewal capabilities mediated also by autocrine NTs loops. Indeed, all NTs, particularly NT-3 and NT-4, have been detected in conditioned medium of different melanoma cell lines (Truzzi et al., 2008). Recent results show that melanoma cells proliferate through autocrine NTs stimulation. K252a significantly reduces melanoma cell proliferation by inhibiting Trks phosphorylation. Proliferation is significantly reduced when endogenous NTs are removed from the culture medium by soluble Trk/Fc receptors. NTs appeared to be important for melanoma cell migration *in vitro*, with special respect for metastatic cell lines. The migratory phenotype is necessarily dependent on the presence of both the high- and low-affinity NTs receptors. Cells treated with p75NTR small interfering RNA (p75NTRsiRNA) fail to respond to NTs stimulation. Similarly, the administration of K252a blocks melanoma cell migration,

confirming that NTs stimulate melanoma cell migration and invasion with the cooperation of the low- and high-affinity receptors (Truzzi et al., 2008).

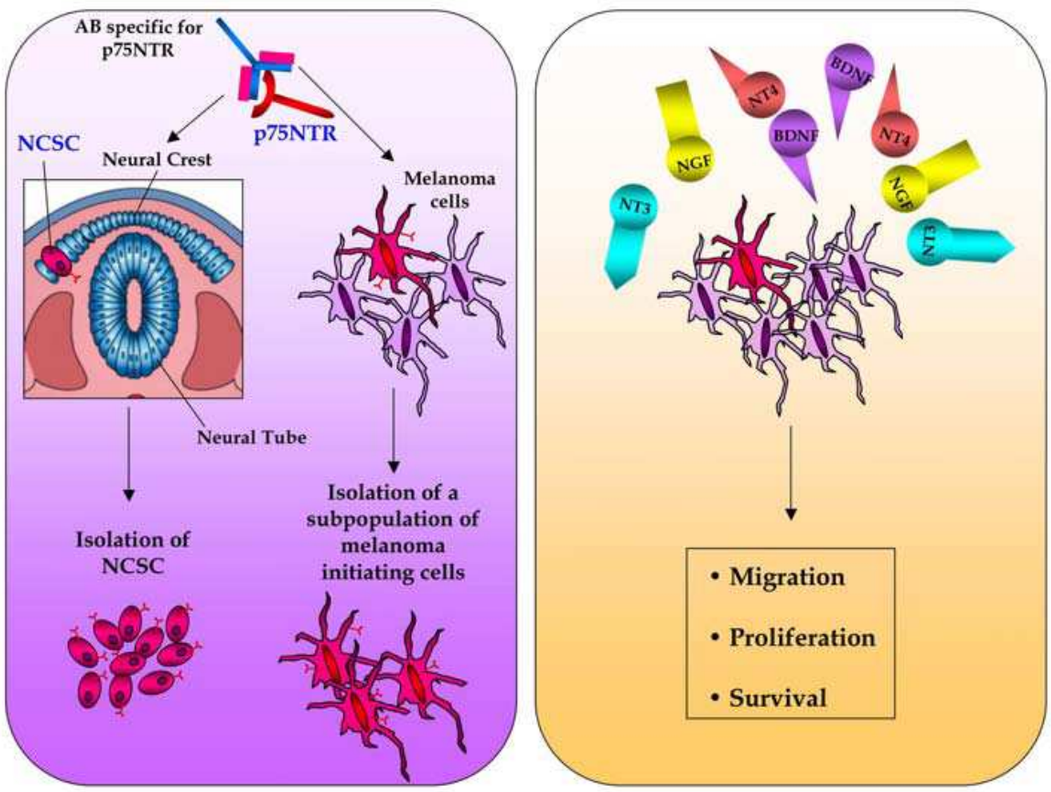


Fig. 3. NTs and their receptors in melanoma biology

Although melanoma may develop in a stepwise manner from a pre-existing lesion, only 26% of melanomas evolve from nevi, while the majority of melanomas arise from normal-appearing skin, suggesting that melanoma development may not follow the classical linear mode of progression (Zabierowsky & Herlyn, 2008). The constant recurrence of melanoma after any therapy is likely due to the survival of a subset of cancer cells that display a resistance to treatment. The "Cancer Stem Cell hypothesis" states that within tumor heterogeneity, only few cells are responsible for tumor initiation and maintenance, sharing with normal stem cells the ability to self renew and to persist in the tissue for years. Although in some tumors, such as leukemia, the CSC model is valid, in melanoma, cells able to initiate tumor formation are not a rare population (Quintana et al., 2010; Held et al., 2010; Roesch et al., 2010). Given the role of NTs and their receptors in melanoma biology, this complex network of growth factors is likely to be involved both in melanoma recurrence and metastasis in the patients. NCSC, that have been proposed as the cells responsible for melanoma origin (see above), have been previously isolated both from neural crest and from adult tissues by using p75NTR (Kruger et al., 2002). Similarly, Boiko and coworkers showed that p75NTR expression characterizes a population of melanoma cells with tumor initiating properties (Boiko et al., 2010). However, the number of cells capable of recapitulating the tumors *in vivo* may vary depending on the assay conditions (Quintana et al., 2008). The use of sensitive mouse models, such as the NOD/SCID IL2R_(null) mice, demonstrated that cell

isolation through p75NTR does not enrich melanoma CSC, and melanoma cells are able to metastasize independently from their expression pattern, being able to reverse their phenotype through clonal expansion (Quintana et al., 2010; Civenni et al., 2011). Consistently, in another study CD34-neg/p75NTR-pos cells from mouse melanomas only rarely form tumors, while the p75NTR-negative counterpart frequently forms tumors, depending on CD34 expression (Held et al., 2010). This suggests that although some lines of evidence point at p75NTR as a good marker for the isolation of melanoma CSC, it may not be the right candidate. It is interesting to mention though that the frequency of p75NTR-positive cells in melanoma samples correlates with higher metastasis and worse patient prognosis (Civenni et al., 2011). Altogether, these results suggest that p75NTR-positive cells are not the CSC population in melanoma, but may retain characteristics of aggressiveness and susceptibility to metastasize. Further characterization of these cells and evaluation of the role of p75NTR in melanoma stem cells is still needed.

6. Conclusions

A significant progress in understanding NTs signaling in skin has been done during the last fiftheen years. Although more studies are needed to better elucidate the role of these molecules in cutaneous physiology and pathology, there is a large body of evidence indicating that NTs form a complex network with autocrine and paracrine functions. In this context, NTs and their receptors seem to play an important role in the origin, development and invasiveness of malignant melanoma. Given the premise and the common neuroectodermal origin of the skin and the nervous system, future studies will allow a better understanding of the cell of origin of melanoma and of the environment that favors the growth and metastasis of the tumor. Translating these data into clinically oriented research will possibly unravel novel strategies for the treatment of melanoma. In particular, blocking Trks will inhibit melanoma cell migration and survival, thus acting in a less toxic and more specific manner, as compared to chemotherapy. Interestingly, Lestaurtinib (CEP-701), a Trk-selective inhibitor, is effective and well tolerated in patients with refractory neuroblastoma (Minturn JE et al., 2011; Evans AE et al., 2001). In addition, inhibitors of Trk kinase activity, such as K-252a family members, have a significant anti-tumor activity in prostatic and pancreatic carcinomas, in preclinical studies.

7. References

Aloe, L.; Tirassa, P. & Lambiase, A. (2008). The topical application of nerve growth factor as a pharmacological tool for human corneal and skin ulcers. *Pharmacol Res*, Vol.57, pp. 253-258.

Anderson, D.J. (2000). Genes, lineages and the neural crest: a speculative review. *Philos Trans R Soc Lond B Biol Sci.* Vol.29; No.355(1399), pp.953-964.

Balch, C.M.; Buzaid, A.C.; Soong, S.J.; Atkins, M.B.; Cascinelli, N.; Coit, D.G.; Fleming, I.D.; Gershenwald, J.E.; Houghton, A. Jr; Kirkwood, J.M.; McMasters, K.M.; Mihm, M.F.; Morton, D.L.; Reintgen, D.S.; Ross, M.I.; Sober, A.; Thompson, J.A. & Thompson, J.F. (2001). Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol*. Vol. 19, No.16, pp. 3635-3648.

Barbacid, M. (1994). The trk family of neurotrophin receptors. *J.Neurobiol,* Vol.25, pp. 1386–1403.

Barde, Y.A.; Edgar, D. & Thoenen, H. (1982). Purification of a new neurotrophic factor from mammalian brain. *EMBO J*, Vol.1, pp. 549-553.

Barker, P.A.; Lomen-Hoerth, C.; Gensch, E.M.; Meakin, S.O.; Glass, D.J. & Shooter, E.M. (1993). Tissue-specific alternative splicing generates two isoforms of the trkA receptor. *J Biol Chem,* Vol.268, pp. 15150–15157.

Beona, C.; Goggins, W.; Quinn, T.; Fullerton, J. & Tsao, H. (2003). Cutaneous melanomas associated with nevi. *Arch Dermatol*, Vol.139, No.12, pp. 1620-1624.

Boiko, A.D.; Razorenova, O.V.; van de Rijn, M.; Swetter, S.M.; Johnson, D.L.; Ly, D.P.; Butler, P.D.; Yang, G.P.; Joshua, B.; Kaplan, M.J.; Longaker, M.T. & Weissman, I.L. (2011). Human melanoma-initiating cells express neural crest nerve growth factor receptor CD271. *Nature.* Vol.470, No.7334, pp. 424.

Botchkarev, V.A.; Metz, M.; Botchkareva, N.V.; Welker, P.; Lommatzsch, M.; Renz, H. & Paus, R. (1999). Brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4 act as "epitheliotrophins" in murine skin. *Lab Invest*, Vol.79, pp. 557-572.

Botchkarev, V.A.; Yaar, M.; Peters, E.M.; Raychaudhuri, S.P.; Botchkareva, N.V.; Marconi, A.; Raychaudhuri, S.K.; Paus, R. & Pincelli, C. (2006). Neurotrophins in skin biology and pathology. *J Invest Dermatol*, Vol.126, No.8, pp.1719-1727.

Brodeur, G.M.; Minturn, J.E.; Ho, R.; Simpson, A.M.; Iyer, R.; Varala, C.R.; Light, J.E.; Kolla, V. & Evans, A.E. (2009). Trk receptor expression and inhibition in neuroblastomas. *Clin Cancer Res*, Vol.15, pp. 3244–3250.

Bunone, G.; Margotti, A.; Compagni, A.; Moranti, E. & Della Valle, G. (1997). Induction of apoptosis by p75 neurotrophin receptor in human neuroblastoma cells. *Oncogene*, Vol.14, pp. 1463–1470.

Chao, M.V. & Hempstead, B.L. (1995). p75 and Trk: a tworeceptor system. *Trends Neurosi*, Vol.18, pp. 321–326.

Civenni, G.; Walter, A.; Kobert, N.; Mihic-Probst, D.; Zipser, M.; Belloni, B.; Seifert, B.; Moch, H.; Dummer, R.; van den Broek, M. & Sommer, L. (2011). Human CD271-Positive Melanoma Stem Cells Associated with Metastasis Establish Tumor Heterogeneity and Long-Term Growth. *Cancer Res.* Epub ahead of print

Clary, D.O. & Reichardt, L.F. (1994). An alternatively spliced form of the nerve growth factor receptor TrkA confers an enhanced response to neurotrophin 3. *Proc Natl Acad Sci U S A*, Vol.91, pp. 11133-11137.

Crowson, A.N.; Magro, C.; Miller, A. & Mihm, M.C. Jr. (2007). The molecular basis of melanomagenesis and the metastatic phenotype. *Semin Oncol.* Vol.34, No.6, pp.476-490.

Cui, J.; Shen, L.Y. & Wang, G.C. (1991). Role of hair follicles in the repigmentation of vitiligo. *J Invest Dermatol.* Vol.97, No.3, pp. 410-416.

Dasari, V.R.; Spomar, D.G.; Li L.; Gujrati, M.; Rao, J.S. & Dinh, D.H. (2008). Umbilical cord blood stem cell mediated downregulation of fas improves functional recovery of rats after spinal cord injury, *Neurochem. Res*, Vol.33, pp. 134–149.

Davis, B.M.; Fundin, B.T.; Albers, K.M.; Goodness, T.P.; Cronk, K.M. & Rice, F.L. (1997). Overexpression of nerve growth factor in skin causes preferential increases among innervation to specific sensory targets. *J Comp Neurol,* Vol.387, pp. 489-506.

Delmas, V.; Beermann, F.; Martinozzi, S.; Carreira, S.; Ackermann, J.; Kumasaka, M.; Denat, L.; Goodall, J.; Luciani, F.; Viros, A.; Demirkan, N.; Bastian, B.C.; Goding, C.R. &

Larue, L. Beta-catenin induces immortalization of melanocytes by suppressing p16INK4a expression and cooperates with N-Ras in melanoma development. *Genes Dev*. Vol.21, No.22, pp. 2923-2935.

Di Marco, E.; Marchisio, P.C.; Bondanza, S.; Franzi, A.T.; Cancedda, R. & De Luca, M. (1991). Growth-regulated synthesis and secretion of biologically active nerve growth factor by human keratinocytes. *J Biol Chem*, Vol.266, pp. 21718-21722.

Di Marco, E.; Mathor, M.; Bondanza, S.; Cutuli, N.; Marchisio, P.C.; Cancedda, R. & De Luca, M. (1993). Nerve growth factor binds to normal human keratinocytes through high and low affinity receptors and stimulates their growth by a novel autocrine loop. *J Biol Chem*, Vol.268, pp. 22838-22846.

Dupin, E.; Glavieux, C.; Vaigot, P. & Le Douarin, N.M. (2000). Endothelin 3 induces the reversion of melanocytes to glia through a neural crest-derived glial-melanocytic progenitor. *Proc Natl Acad Sci USA*, Vol.97, No.14, pp.7882-7887.

Eggert, A.; Sieverts, H.; Ikegaki, N. & Brodeur, G.M. (2000). p75 mediated apoptosis in neuroblastoma cells is inhibited by expression of TrkA. *Med Pediatr Oncol*, Vol.35, pp. 573–576.

Falabella, R., & Barona, M.I. (2009). Update on skin repigmentation therapies in vitiligo. *Pigment Cell Melanoma Res.* Vol.22, No.1, pp.42-65.

Flørenes, V.A.; Maelandsmo, G.M.; Holm, R.; Reich, R.; Lazarovici, P. & Davidson, B. (2004). Expression of activated TrkA protein in melanocytic tumors: relationship to cell proliferation and clinical outcome. *Am J Clin Pathos*, Vol.122, pp. 412–420.

Fischer, T.C.; Lauenstein, H.D.; Serowka, F.; Pilzner, C.; Groneberg, D.A. & Welker, P. (2008). Pan-neurotrophin receptor p75NTR expression is strongly induced in lesional atopic mast cells. *Clin Exp Allergy,* Vol.38, pp. 1168-1173

Frade, J.M & Barde, Y.A. (1998). Nerve growth factor: two receptors, multiple functions. *Bioessays*, Vol. 20, pp. 137-145.

Garbe, C.; Eigentler, T.K.; Keilholz, U.; Hauschild, A. & Kirkwood, J.M. (2011). Systematic review of medical treatment in melanoma: current status and future prospects. *Oncologist.* Vol.16, No.1, pp. 5-24.

Geiger, T.R.; Song, J.Y.; Rosado, A. & Peeper, D.S. (2011). Functional Characterization of Human Cancer-Derived TRKB Mutations. *PLoS One,* Vol.6, No.2, pp. e16871.

Gershon, T.R.; Oppenheimer, O.; Chin, S.S. & Gerald, W.L. (2005). Temporally regulated neural crest transcription factors distinguish neuroectodermal tumors of varying malignancy and differentiation. *Neoplasia.* Vol.7, No.6, pp.575-84.

Greene, L.A. & Kaplan, D.R. (1995). Early events in neurotrophin signalling via Trk and p75 receptors. *Curr Opin Neurobiol*, Vol.5, pp. 579–587.

Guiton, M., Gunn-Moore, F. J., Glass, D. J., Geis, D. R., Yancopoulos, G. D. & Tavare, J. M. (1995). Naturally occurring tyrosine kinase inserts block high affinity binding of phospholipase C gamma and Shc to TrkC and neurotrophin-3 signaling. *J. Biol. Chem*, Vol.270, No.20, pp. 384–390.

He, X.L. & Garcia, K.C. (2004). Structure of nerve growth factor complexed with the shared neurotrophin receptor p75. *Sciente*, Vol.304, pp. 870-875.

Held, M.A.; Curley, D.P.; Dankort, D.; McMahon, M.; Muthusamy, V. & Bosenberg, M.W. (2010). Characterization of melanoma cells capable of propagating tumors from a single cell. *Cancer Res*, Vol.70, No.1, pp. 388-397.

Hempstead, B.L.; Rabin, S.J.; Kaplan, L.; Reid, S.; Parada, L.F. & Kaplan, D.R. (1992). Overexpression of the trk tyrosine kinase rapidly accelerates nerve growth factor-induced differentiation. *Neuron*, Vol.9, pp. 883–896.

Hoek, K.S. & Godine, C.R. (2010). Cancer stem cells versus phenotype-switching in melanoma. *Pigment Cell Melanoma Res.*, Vol.23, No.6, pp.746-759.

Huang, E.J. & Reichardt, L.F. (2003). Trk receptors: roles in neuronal signal transduction. *Annu Rev Biochem*; Vol. 72, pp. 609-642.

Huttenbach, Y.; Prieto, V.G. & Reed, J.A. (2002). Desmoplastic and spindle cell melanomas express protein markers of the neural crest but not of later committed stages of Schwann cell differentiation. *J Cutan Pathos,* Vol.29, pp. 562-568.

Kaplan, D.R. & Miller, F.D. (2004). Neurobiology: a move to sort life from death. *Nature*, Vol.427, pp. 798-799.

Kinkelin, I.; Stucky, C.L. & Koltzenburg, M. (1999). Postnatal loss of Merkel cells, but not of slowly adapting mechanoreceptors in mice lacking the neurotrophin receptor p75. *Eur J Neurosi*, Vol.11, pp. 3963-3969.

Iwamoto, S.; Burrows, R.C.; Agoff, S.N.; Piepkorn, M.; Bothwell, M. & Schmidt, R. (2001). The p75 neurotrophin receptor, relative to other Schwann cell and melanoma markers, is abundantly Expressed in spindled melanomas. *Am J Dermatopathol*, Vol.23, pp. 288-294.

Indo, Y. (2001). Molecular basis of congenital insensitivity to pain with anhidrosis (CIPA): mutations and polymorphisms in TRKA (NTRK1) gene encoding the receptor tyrosine kinase for nerve growth factor. *Hum Mutat*, Vol.18, pp. 462-471.

Ingraham, C.A.; Wertalik, L. & Schor, N.F. (2011). Necdin and neurotrophin receptors: interactors of relevance for neuronal resistance to oxidant stress. *Pediatr Res,* Vol.69, No.4, pp. 279-284.

Johnsen, J.I.; Kogner, P.; Albihn, A. & Henriksson, M.A. (2009). Embryonal neural tumours and cell death. *Apoptosis*, Vol.14, pp. 424–438.

Kanik, A.B.; Yaar, M. & Bhawan, J. (1996). P75 nerve growth factor receptor staining helps identify desmoplastic and neurotropic melanoma. *J Cutan Pathol*, Vol.23, pp. 205-210.

Kim, J.Y.; Sutton, M.E.; Lu, D.J.; Cho, T.A.; Goumnerova, L.C.; Goritchenko, L.; Kaufman, J.R.; Lam, K.K.; Billet, A.L.; Tarbell, N.J.; Wu, J.; Allen, J.C.; Stiles, C.D.; Segal, R.A. & Pomeroy, S.L. (1999). Activation of neurotrophin-3 receptor TrkC induces apoptosis in medulloblastomas. *Cancer Res*, Vol.59, pp. 711–719.

Kruger, G.M.; Mosher, J.T.; Bixby, S.; Joseph, N.; Iwashita, T.; Morrison, S.J. (2002). Neural crest stem cells persist in the adult gut but undergo changes in self-renewal, neuronal subtype potential, and factor responsiveness. *Neuron,* Vol.35, No.4, pp. 657-669.

Krüttgen, A.; Schneider, I. & Weis, J. (2006). The dark side of the NGF family: neurotrophins in neoplasias. *Brain Pathol,* Vol.16, No.4, pp. 304-310.

Landi, F.; Aloe, L.; Russo, A.; Cesari, M.; Onder, G.; Bonini, S.; Carbonin, P.U. & Bernabei, R. (2003). Topical Treatment of Pressure Ulcers with Nerve Growth Factor. A Randomized Clinical Trial. *Ann Int Med*, Vol.139 , No.8, pp. 635-641.

Langtimm-Sedlak, C.J.; Schroeder, B.; Saskowski, J.L.; Carnahan, J.F.; & Sieber-Blum, M. (1996). Multiple actions of stem cell factor in neural crest cell differentiation in vitro. *Dev Biol,* Vol.174, No.2, pp. 345-359.

Lazova, R.; Tantcheva-Poor, I. & Sigal, A.C. (2010). p75 nerve growth factor receptor staining is superior to S100 in identifying spindle cell and desmoplastic melanoma. *J Am Acad Dermatol*, Vol.63, pp. 852-858.

Levi-Montalcini, R. (1987). The nerve growth factor 35 years later. *Sciente*, Vol.237, pp. 1154-1162.

Li, L.; Fukunaga-Kalabis, M.; Yu, H.; Xu, X.; Kong, J.; Lee, J.T. & Herlyn, M. (2010). Human dermal stem cells differentiate into functional epidermal melanocytes. *J Cell Sci*, Vol.123, pp. 853-860.

Lu, B.; Pang, P.T. & Woo, N.H. (2005). The yin and yang of neurotrophin action. *Nat Rev Neurosi*, Vol.6, No8, pp. 603-614.

Luberg, K.; Wong, J.; Weickert, C.S. & Timmusk, T. (2010). Human TrkB gene: novel alternative transcripts, protein isoforms and expression pattern in the prefrontal cerebral cortex during postnatal development. *J Neurochem*, Vol.113, pp. 952-964.

Lugassy, C. & Barnhill, R.L. (2007). Angiotropic melanoma and extravascular migratory metastasis: a review. *Adv Anat Pathol.* Vol.14, No.3, pp. 195-201.

Marconi, A.; Vaschieri, C.; Zanoli, S.; Giannetti, A. & Pincelli, C. (1999). Nerve growth factor protects human keratinocytes from ultraviolet-B-induced apoptosis. *J Invest Dermatol*, Vol.113, pp. 920-927.

Marconi, A.; Terracina, M.; Fila, C.; Franchi, J.; Bonté, F.; Romagnoli, G.; Maurelli, R.; Failla, C.M.; Dumas, M. & Pincelli, C. (2003). Expression and function of neurotrophins and their receptors in cultured human keratinocytes. *J Invest Dermatol*, Vol.121, pp. 1515-21. Erratum in: J Invest Dermatol 2004; 123:803.

Marconi, A.; Panza, M.C.; Bonnet-Duquennoy, M.; Lazou, K.; Kurfurst, R.; Truzzi, F.; Lotti, R.; De Santis, G.; Dumas, M.; Bonté, F. & Pincelli, C. (2006). Espression and function of neurotrophins and their receptors in human melanocytes. *Int.J Cosmet Sci*, Vol.28, pp. 255-261.

Marchetti, D.; Denkins, Y.; Reiland, J.; Greiter-Wilke, A.; Galjour, J.; Murry, B.; Blust, J. & Roy, M. (2003). Brain-metastatic melanoma: a neurotrophic perspective. *Pathol Oncol Res*, Vol.9, pp. 147–158

Marshall, J.S.; Gomi, K.; Blennerhassett, M.G. & Bienenstock, J. (1999). Nerve growth factor modifies the expression of inflammatory cytokines by mast cells via a prostanoid-dependent mechanism. *J Immunol*, Vol.162, pp. 4271-4276.

Micera, A.; Vigneti, E.; Pickholtz, D.; Reich, R.; Pappo, O.; Bonini, S.; Maquart, F.X.; Aloe, L. & Levi-Schaffer, F. (2001). Nerve growth factor displays stimulatory effects on human skin and lung fibroblasts, demonstrating a direct role for this factor in tissue repair. *Proc Natl Acad Sci USA*, Vol.98, pp. 6162-6167.

Micera, A.; Lambiase, A.; Stampachiacchiere, B.; Sgrulletta, R.; Normando, E.M.; Bovini, S. & Bovini, S. (2007b). Nerve growth factor has a modulatory role on human primary fibroblast cultures derived from vernal keratoconjunctivitis-affected conjunctiva. *Mol Vis*, Vol.13, pp. 981-987.

Montaño, J.A.; Pérez-Piñera, P.; García-Suárez, O.; Cobo, J. & Vega, J.A. (2010). Development and neuronal dependence of cutaneous sensory nerve formations: Lessons from neurotrophins. *Microsc Res Tech*, Vol.73, pp. 513-529.

Murray, S.S.; Perez, P.; Lee, R. Hempstead, B.L. & Chao, M.V. (2004). A novel p75 neurotrophin receptor-related protein, NRH2, regulates nerve growth factor binding to the TrkA receptor. *J Neurosi*, Vol.24, pp. 2742-2749.

Nakagawara, A.; Arima-Nakagawara, M.; Scavarla, N.J.;. Azar, C.G.; Cantor, A.B. & Brodeur, G.M. (1993). Association between high levels of expression of the Trk gene and favorable outcome in human neuroblastomas *N. Engl. J. Med.,* Vol.328, pp. 847–854.

Nakagawara, A. (2001). Trk receptor tyrosine kinases: a bridge between cancer and neural development, *Cancer Lett*, Vol.169, pp.107–114.

Nishikawa, S. & Osawa, M. (2007). Generating quiescent stem cells. *Pigment Cell Res*, Vol.20, No.4, pp. 263-270.

Nishimura, E.K.; Jordan, S.A.; Oshima, H.; Yoshida, H.; Osawa, M.; Moriyama, M.; Jackson, I.J.; Barrandon, Y.; Miyachi, Y. & Nishikawa, S. (2002). Dominant role of the niche in melanocyte stem-cell fate determination. *Nature*, Vol.416, No.6883, pp. 854-860.

Nykjaer, A.; Lee, R.; Teng, K.K.; Jansen, P.; Madsen, P.; Nielsen, M.S.; Jacobsen, C.; Kliemannel, M.; Schwarz, E.; Willnow, T.E.; Hempstead, B.L. & Petersen, C.M. (2004). Sortilin is essential for proNGF-induced neuronal cell death. *Nature*, Vol.427, No.6977, pp. 843-848.

Ohta, T.; Watanabe, T.; Katayama, Y.; Kurihara, J.; Yoshino, A.; Nishimoto, H. & Kishimoto, H. (2006). TrkA expression is associated with an elevated level of apoptosis in classic medulloblastomas. *Neuropathology*, Vol.26, pp. 170–177.

Palazzo, E.; Marconi, A.; Truzzi, F.; Dallaglio, K.; Petrachi, T.; Humbert, P.; Schnebert, S.; Perrier, E.; Dumas, M. & Pincelli, C. (2011). Role of neurotrophins on dermal fibroblast survival and differentiation. *J Cell Physiol.,* doi: 10.1002/jcp.22811.

Papatsoris, A.G.; Liolitsa, D. & Deliveliotis, C. (2007). Manipulation of the nerve growth factor network in prostate cancer. *Expert Opin Investig Drugs,* Vol.16, No.3, pp. 303-309.

Paratore, C.; Goerich, D.E.; Suter, U.; Wegner, M. & Sommer, L. (2001). Survival and glial fate acquisition of neural crest cells are regulated by an interplay between the transcription factor Sox10 and extrinsic combinatorial signaling. *Development*, Vol.128, No.20, pp. 3949-3961.

Paus, R.; Lüftl, M. & Czarnetzki, B.M. (1994). Nerve growth factor modulates keratinocyte proliferation in murine skin organ culture. *Br J Dermatol*, Vol.130, pp. 174-180.

Peacocke, M.; Yaar, M.; Mansur, C.P.; Chao, M.V. & Gilchrest, B.A. (1988). Induction of nerve growth factor receptor on cultured human melanocytes. *Proc Natl Acad Sci USA*, Vol.85, pp. 5282-5286.

Perez-Pinera, P.; García-Suarez, O.; Germanà, A.; Díaz-Esnal, B.; de Carlos, F.; Silos-Santiago, I.; del Valle, M.E.; Cobo,J. & Vega, J.A. (2008). Characterization of sensory deficits in TrkB knockout mice. *Neurosci Lett*, Vol.433, pp. 43-47.

Perlis, C. & Herlyn, M. (2004). Recent advances in melanoma biology. *Oncologist*, Vol.9, pp.182–187.

Pincelli, C.; Fantini, F. & Giannetti, A. (1994). Nerve growth factor and the skin. *Int J Fermato,* Vol.33, pp. 308-312.

Pincelli, C.; Haake, A.R.; Benassi, L.; Grassilli, E.; Magnoni, C.; Ottani, D.; Polakowska, R.; Franceschi, C. & Giannetti, A. (1997). Autocrine nerve growth factor protects human keratinocytes from apoptosis through its high affinity receptor (TRK): a role for BCL-2. *J Invest Dermatol*, Vol.109, pp. 757-764.

Quintana, E.; Shackleton, M.; Sabel, M.S.; Fullen, D.R.; Johnson, T.M. & Morrison, S.J. (2008). Efficient tumour formation by single human melanoma cells. *Nature*, Vol.456, No.7222, pp. 593-598.

Quintana, E.; Shackleton, M.; Foster, H.R.; Fullen, D.R.; Sabel, M.S.; Johnson, T.M. & Morrison, S.J. (2010). Phenotypic heterogeneity among tumorigenic melanoma cells from patients that is reversible and not hierarchically organized. *Cancer Cell*, Vol.18, No.5, pp. 510-523.

Real, C.; Glavieux-Pardanaud, C.; Le Douarin, N.M. & Dupin, E. (2006). Clonally cultured differentiated pigment cells can dedifferentiate and generate multipotent progenitors with self-renewing potential. *Dev Biol*, Vol.300, No.2, pp.656-669.

Reichardt, L.F. (2006). Neurotrophin-regulated signalling pathways. *Philos Trans R Soc Lond B Biol Sci*, Vol.361, pp.1545–1564.

Rifkin, J.T.; Todd, V.J.; Anderson, L.W. & Lefcort, F. (2000). Dynamic expression of neurotrophin receptors during sensory neuron genesis and differentiation. *Dev Biol*. Vol.227, No.2, pp. 465-480.

Rodriguez-Tébar, A.; Dechant, G. & Barde, Y.A. (1990). Binding of brain-derived neurotrophic factor to the nerve growth factor receptor. *Neuron*, Vol.4, pp. 487-492.

Roesch, A.; Fukunaga-Kalabis, M.; Schmidt, E.C.; Zabierowski, S.E.; Brafford, P.A.; Vultur, A.; Basu, D.; Gimotty, P.; Vogt, T. & Herlyn, M. (2010). A temporarily distinct subpopulation of slow-cycling melanoma cells is required for continuous tumor growth. *Cell*, Vol.141, pp. 583–594.

Rogers, M.L.; Beare, A.; Zola, H. & Rush, R.A. (2008). CD 271 (P75 neurotrophin receptor). *J Biol Regul Homeost Agents.* Vol.22, No.1, pp. 1-6.

Roux, P.P. & Barker, P.A. (2002). Neurotrohin signaling through the p75 neurotrophin receptor. *Prog Neurobiol*, Vol.67, pp. 203–233.

Sabatino, M.; Stroncek, D.F.; Klein, H.; Marincola, F.M. & Wang, E. (2009). Stem cells in melanoma development. *Cancer Lett.*, Vol.279, No.2, pp. 119-125.

Segal, R.A. (2003). Selectivity in neurotrophin signaling: theme and variations. *Annu Rev Neurosi*, Vol.26, pp. 299-330.

Segal, R.A.; Goumnerova, L.C.; Kwon, Y.K.; Stiles, C.D. & Pomeroy, S.L. (1994). Expression of the neurotrophin receptor TrkC is linked to a favorable outcome in medulloblastoma. *Proc Natl Acad Sci U S A*. Vol.91, No.26, pp. 12867-12871.

Shonukan, O.; Bagayogo, I.; McCrea, P.; Chao, M. & Hempstead, B. (2003). Neurotrophin-induced melanoma cell migration is mediated through the actin-bundling protein fascin. *Oncogene*, Vol.22, pp. 3616-3623.

Sieber-Blum, M. & Grim, M. (2004). The adult hair follicle: cradle for pluripotent neural crest stem cells, *Birth Defects Res. C: Embryo Today*, Vol.72 , No.2, pp. 162–172.

Sieber-Blum, M.; Grim, M.; Hu, Y.F. & Szeder, V. (2004). Pluripotent neural crest stem cells in the adult hair follicle. *Dev. Dyn*, Vol.231, pp. 258–269.

Stefanato, C.M.; Yaar, M.; Bhawan, J.; Philips, T.J.; Kosmadaki, M.G.; Botchkarev, V. & Gilchrest, B.A. (2003). Modulations of nerve growth factor and Bcl-2 in ultraviolet-irradiated human epidermis. *J Cutan Pathos*, Vol.30, pp. 351-357.

Stemple, D.L. & Anderson, D.J. (1992). Isolation of a stem cell for neurons and glia from the mammalian neural crest. *Cell,* Vol.71, No.6, pp. 973-985.

Sun, W.; Lin, H.; Chen, B.; Zhao, W.; Zhao, Y.; Xiao, Z. & Dai, J. (2010). Collagen scaffolds loaded with collagen-binding NGF-beta accelerate ulcer healing. *J Biomed Mater Res A*, Vol.92, pp. 887-895.

Szeder, V.; Grim, M.; Kucera, J. & Sieber-Blum, M. (2003). Neurotrophin-3 signaling in mammalian Merkel cell development. *Dev Dyn,* Vol. 228, pp. 623-629.

Strohmaier, C.; Carter, B.D.; Urfer, R.; Barde, Y.A. & Dechant, G. (1996). A splice variant of the neurotrophin receptor trkB with increased specificity for brain-derived neurotrophic factor. *EMBO J*, Vol.15, pp. 3332-3337.

Tacconelli, A.; Farina, A.R.; Cappabianca, L.; Gulino, A. & Mackay, A.R. (2005). TrkAIII. A novel hypoxia-regulated alternative TrkA splice variant of potential physiological and pathological importance. *Cell Cycle*, Vol.4, pp. 8–9.

Tauszig-Delamasure, S.; Yu, L.Y.; Cabrera, J.R.; Bouzas-Rodriguez, J.; Mermet-Bouvier, C.; Guix, C.; Bordeaux, M.C.; Arumäe, U. & Mehlen, P. (2007). The TrkC receptor induces apoptosis when the dependence receptor notion meets the neurotrophin paradigm. *Proc Natl Acad Sci USA*, Vol.14, No.104, pp.13361-13366.

Teng, K.K. & Hempstead, B.L. (2004). Neurotrophins and their receptors: Signaling trios in complex biological systems. *Cell Mol Life Sci*, Vol.61, pp.35–48.

Thiele, C.J.; Li, Z. & McKee, A.E. (2009). On Trk--the TrkB signal transduction pathway is an increasingly important target in cancer biology. *Clin Cancer Res*, Vol.15, No.19, pp. 5962-5967.

Tiberio, R.; Marconi, A.; Fila, C.; Fumelli, C.; Pignatta, M.; Krajewski, S.; Giannetti, A.; Reed, J.C. & Pincelli, C. (2002). Keratinocytes enriched for stem cells are protected from anoikis via an integrin signaling pathway in a Bcl-2 dependent manner. *FEBS Lett*, Vol.524, pp. 139-144.

Tron, V.A.; Coughlin, M.D.; Jang, D.E.; Stanisz, J. & Sauder, D.N. (1990). Expression and modulation of nerve growth factor in murine keratinocytes (PAM 212). *J Clin Invest,* Vol.85, pp. 1085.

Truzzi, F.; Marconi, A.; Lotti, R.; Dall'aglio, K.; French, L.E. & Hempstead, B.L. & Pincelli, C. (2008). Neurotrophins and their receptors stimulate melanoma cell proliferation and migration. *J Invest Dermatol*, Vol.128, pp. 2031-2040.

Truzzi, F.; Marconi, A.; Atzei, P.; Panza, M.C.; Lotti, R.; Dall'aglio, K.; Tiberio, R.; Palazzo, E.; Vaschieri C. & Pincelli, C. p75 neurotrophin receptor mediates apoptosis in transit-amplifying cells and its overexpression restores cell death in psoriatic keratinocytes. *Cell Death Differ*. (2011) Vol.18, pp. 948-958.

Ultsch, M.H.; Wiesmann, C.; Simmons, L.C.; Henrich, J.; Yang, M.; Reilly, D.; Bass, S.H. & de Vos,A.M. (1999). Crystal structures of the neurotrophin-binding domain of TrkA, TrkB and TrkC. *J Mol Biol*, Vol.290, pp.149-159.

Yeo, G.S.; Conie Hung, C.C.; Rochford, J.; Keogh. J.; Gray, J.; Sivaramakrishnan, S.; O'Rahilly, S. & Faroogi, I.S. (2004). A de novo mutation affecting human TrkB associated with severe obesity and developmental delay. *Nat Neurosi*, Vol.7, pp. 1187-1189.

Walch, E.T.; Albino, A.P. & Marchetti, D. (1999). Correlation of overexpression of the low-affinity p75 neurotrophin receptor with augmented invasion and heparanase production in human malignant melanoma cells. *Int J Cancer*, Vol.82, pp. 112–120.

Wang, J.J.; Tapinat, A.; Ethell, D.W.; Testa, M.P. & Bredesen, D.E. (2000). Phosphorylation of the common neurotrophin receptor p75 by p38beta2 kinase affects NF-kappaB and AP-1 activities. *J Mol Neurosi*, Vol.15, pp. 19-29.

Yaar, M.; Grossman, K.; Eller, M. & Gilchrest, B.A. (1991). Evidente for nerve growth factor-mediated paracrine effects in human epidermis. *J Cell Biol*, Vol.115, pp. 821-828.

Yaar, M., Eller, M.S.; DiBenedetto, P.; Reenstra, W.R.; Zhai, S.; McQuaid, T.; Archambault, M. & Gilchrest, B.A. (1994). The trk family of receptors mediates nerve growth

factor and neurotrophin-3 effects in melanocytes. *J Clin Invest.*, Vol.94, pp. 1550-1562.

Yamashiro, D.J.; Nakagawara, A.; Ikegaki, N.; Liu, X.G. & Brodeur, G.M. (1996). Expression of TrkC in favorable human neuroblastomas. *Oncogene*, Vol.12, pp. 37–41.

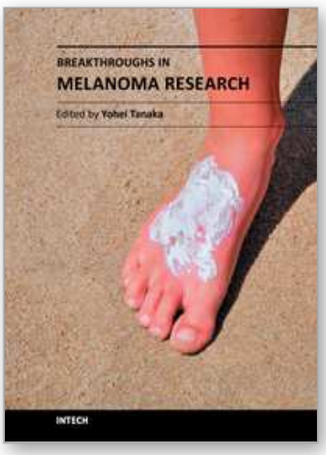
Yu, H.; Fang, D.; Kumar, S. M.; Li, L.; Nguyen, T. K.; Acs, G.; Herlyn, M. & Xu, X. (2006). Isolation of a novel population of multipotent adult stem cells from human hair follicles. *Am. J. Pathos*, Vol.168, pp. 1879-1888.

Zabierowski, S.E. & Herlyn, M. (2008). Learning the ABCs of melanoma-initiating cells. *Cancer Cell*. Vol.13, No.3, pp.185-187.

Zhai, S.; Yaar, M.; Doyle, S.M. & Gilchrest, B.A. (1996). Nerve growth factor rescues pigment cells from ultraviolet-induced apoptosis by upregulating BCL-2 levels. *Exp Cell Res*, pp. 224-335.

Zhang, J.M.; Hoffmann, R. & Sieber-Blum, M. (1997). Mitogenic and anti-proliferative signals for neural crest cells and the neurogenic action of TGF-beta1. *Dev Dyn*, Vol.208, No.3, pp.375-386.

Wang, Q.; Fang, W.H.; Krupinski, J.; Kumar, S.; Slevin, M. & Kumar, P. (2008). Pax genes in embryogenesis and oncogenesis. *J Cell Mol Med.* Vol.12, No.6A, pp. 2281-2294.



Breakthroughs in Melanoma Research
Edited by Dr Yohei Tanaka

ISBN 978-953-307-291-3
Hard cover, 628 pages
Publisher InTech
Published online 30, June, 2011
Published in print edition June, 2011

Melanoma is considered to be one of the most aggressive forms of skin neoplasms. Despite aggressive researches towards finding treatments, no effective therapy exists to inhibit the metastatic spread of malignant melanoma. The 5-year survival rate of metastatic melanoma is still significantly low, and there has been an earnest need to develop more effective therapies with greater anti-melanoma activity. Through the accomplishment of over 100 distinguished and respected researchers from 19 different countries, this book covers a wide range of aspects from various standpoints and issues related to melanoma. These include the biology of melanoma, pigmentations, pathways, receptors and diagnosis, and the latest treatments and therapies to make potential new therapies. Not only will this be beneficial for readers, but it will also contribute to scientists making further breakthroughs in melanoma research.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Carlo Pincelli, Katiuscia Dallaglio and Francesca Truzzi (2011). Melanoma and the Nervous System – Novel Pathways Mediated by Neurotrophins and Their Receptors, Breakthroughs in Melanoma Research, Dr Yohei Tanaka (Ed.), ISBN: 978-953-307-291-3, InTech, Available from: http://www.intechopen.com/books/breakthroughs-in-melanoma-research/melanoma-and-the-nervous-system-novel-pathways-mediated-by-neurotrophins-and-their-receptors

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen