Review

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The role of nerve growth factor and its receptors in tumorigenesis and cancer pain

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Summary **The nerve growth factor (NGF) is a growth factor that belongs to the neurotrophin family. NGF has two structurally different receptors, the p75 neurotrophin receptor (p75NTR) and the tropomyosin-related kinase A (TrkA). Interaction of NGF with its receptors regulates a variety of physiological processes of neuronal system. Recent studies have shown that NGF and its receptors were involved in the regulation of tumourigenesis by either supporting or suppressing tumor growth depending on the tumor types. This review summarizes the current views of NGF and its receptors in tumorigenesis and cancer pain.**

Keywords: Nerve growth factor, tumorigenesis, cancer pain, p75NTR receptor, TrkA receptor

1. Introduction

Nerve growth factor (NGF) is a growth factor that belongs to the nerve growth factor family of neurotrophin. NGF, like the other neurotrophin family members such as brain derived neurotrophic factor (BDNF), neurotrophins-3 (NT-3), neurotrophins-4/5 (NT-4/5), and neurotrophins-6 (NT-6), binds to two structurally different types of receptors: the p75 neurotrophin receptor (p75NTR) and tropomyosin-related kinase A (TrkA) (Figure 1) (*1-3*) and regulates neuronal survival, differentiation and growth. Currently, NGF, released from the nerve fibers, has been found to be involved in the tumor progression, leading to generate a positive microenvironment for cancer cell survival and proliferation (*4-6*).

2. The molecular structure and physiological function of NGF and its receptors

2.1. *NGF*

NGF was first discovered by Rita Levi-Montalcini in the early 1950's for its effects on the neuronal survival, proliferation, and differentiation (*7-9*). NGF is not only discovered in nervous system, but also detected and quantified in a variety of normal and neoplastic human tissues (*10,11*).

NGF was first isolated from the mouse submaxillary gland with the molecular weight of approximately 140 KD, which is highly homologous to human NGF (*12*). Each NGF is composed of 2 α subunits, 1 β subunit, 2 γ subunits (α2βγ2) and also one or two zinc ions (*13,14*). The β subunit of NGF is a biologically active region and a non-covalently bound homodimer that can be separated into 2 identical chains of 118 amino acids. The 2 γ subunits of NGF have proteolytic activity and are members of the kallikrein family of trypsin-like proteases. The 2 α subunits are highly homologous to the γ subunit but without any enzymatic activity (*15,16*).

Under physiological condition, NGF regulates neuronal survival, proliferation, and differentiation in the peripheral and central nervous systems by binding to its receptors: TrkA and p75NTR. Binding to p75NTR, NGF initiates recruitment of various adaptors, which activate c-Jun N-terminal kinase (JNK) signaling pathways to promote apoptosis, and activate NF-κB pathways to promote cell survival. By binding to TrkA, NGF initiates pro-survival PI3K/AKT and Ras/Raf signaling pathways, *via* Ras/MAPK pathway to promote cell proliferation and metastasis (Figure 2) (*6,17-20*).

The intracellular activation of NGF receptor binding in figure 2 occurs only as receptor homodimers. Researchers have also suggested the existence of p75NTR and TrkA complexes which has been presented

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from both cross-linking and immunoprecipitation (*21*). Previous research has shown that p75NTR and TrkA interact directly in surface membranes or their extracellular (EC) domains (*22*), but the latest research shows that TrkA and p75NTR associate physically through their intracellular (IC) domains (*23*). Regardless of how p75NTR and TrkA receptors associate, the coexpression of p75NTR and TrkA receptors results in the formation of high-affinity NGF binding sites. The reason is associated with p75NTR, which can contribute to increase the binding rate of NGF with TrkA and enhance TrkA activation and the number of high affinity binding sites (*24*). A recent report demonstrated that an endogenous intracellular domain fragment of p75NTR containing these 29 amino acids was capable of interacting with TrkA resulting in the formation of high-affinity binding sites for NGF (*25*). The formation of high-affinity binding sites, resulting in enhanced NGF responsiveness, is also necessary for complete outgrowth and for long-term survival (*26,27*).

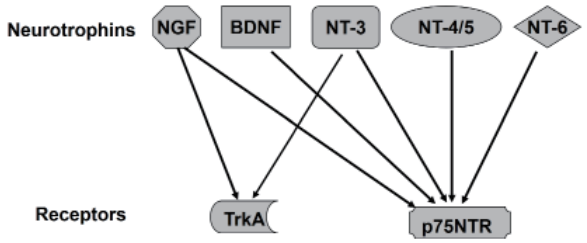

Figure 1. Neurotrophins and their preferred receptors. Neurotrophins all bind to p75NTR. TrkA is the preferred receptor for NGF. The interaction of NT-3 with TrkA requires high concentrations of the neurotrophin.

For a long time, NGF is always considered to be the main form for its biological activity in regulating neuronal survival, proliferation, and differentiation. However, recent studies showed that proNGF, the precursor form of NGF, is really largely exist in central nervous system tissues, and has biological functions exceeding its role as a precursor (*17,28,29*). ProNGF could induce cell death by binding to p75NTR with high affinity (*30-32*). But it shows low affinity to TrkA, another receptor of NGF (33). Moreover, proNGF could induce apoptosis by binding to p75NTR and sortilin, a specific receptor of proNGF. Sortilin is a member of the mammalian type-I transmembrane receptors containing a Vps10p domain, which palys an essential role in proNGF-induced cell death and apoptosis (*34,35*). Blocking sortilin can prevent induction of apoptosis by proNGF (*36*). Further studies showed that sortilin acted as an assistant receptor and molecular switch for p75NTR-mediated apoptosis induced by proNGF (*37*). This indicated that proNGF induced apoptosis by forming a stable ternary proNGF/sortilin/p75NTR complex instead of proNGF/p75NTR complex (*34,38*).

2.2. *NGF receptors*

p75NTR is a low affinity NGF receptor and also a member of the tumor necrosis factor (TNF) receptor superfamily. It has no tyrosine kinase activity, nor is it linked to a G-protein-coupled pathway (*39*). p75NTR consists of an extracellular region, which contains four cysteine-rich domains, a single transmembrane domain and an intracellular death domain. Its intracellular

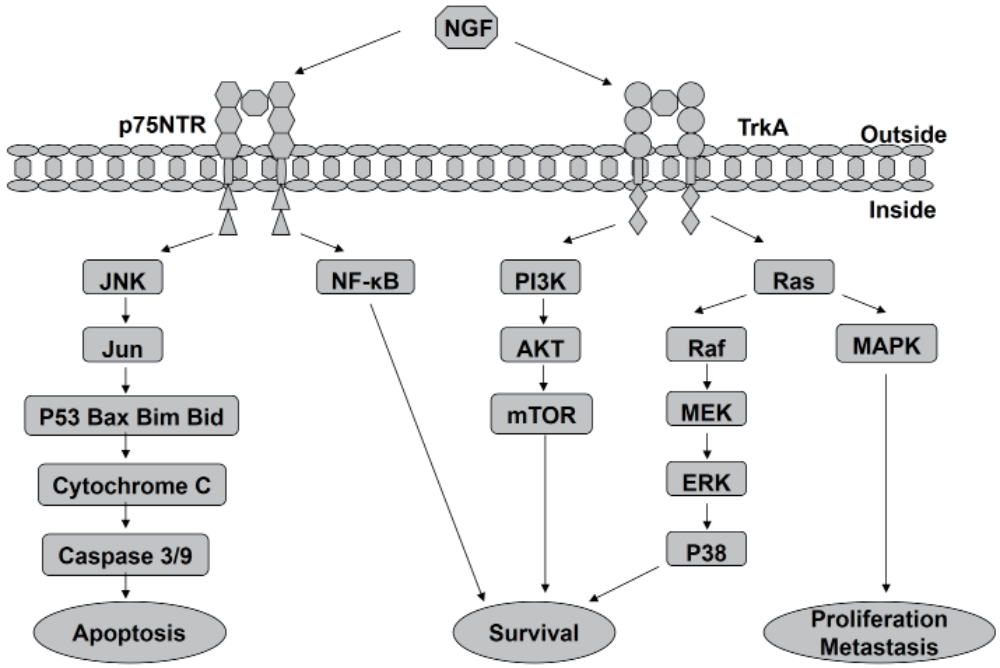

Figure 2. NGF signalling pathways. p75NTR and TrkA signalling pathways. "→" represents stimulatory modification.

domain can be phosphorylated and bind to a number of death-signalling proteins (*40,41*).

TrkA is a high affinity NGF receptor with tyrosine kinase activity. Unlike p75NTR which can be activated by all neurotrophin family members, TrkA is activated only by particular neurotrophins (Figure 1) (*40,42-44*). Like most receptor tyrosine kinases, TrkA is activated by ligand-induced formation of non-covalently associated receptor dimers (*43*). TrkA primarily regulates growth and differentiation of neurons in both peripheral and central nervous systems. NGF/TrkA signaling pathway supports survival and differentiation of sympathetic as well as sensory neurons responsive to temperature and pain (*45*).

3. Involvement of NGF and its receptors in cancer

3.1. *The possible role in tumorigenesis*

3.1.1. *NGF prevents tumor growth through regulating innervations of perivascular nerve*

Tumors require sustenance in the form of nutrients and oxygen and as well as an ability to evacuate metabolic wastes and carbon dioxide. The tumor-associated neovasculature, generated by the process of angiogenesis, addresses these needs (*46*). Growth of solid tumors is also dependent on their blood supply which is derived from two sources: blood vessels recruited from the pre-existing host vascular network and those resulting from the angiogenic response to cancer cells (*47*).

NGF facilitates innervations of perivascular nerve to regulate the blood flow in tumor neovessels and suppress tumor growth. Goda *et al*. demonstrated that NGF administration subcutaneously suppressed the growth of DU145 prostate tumors in nude mice by accelerating the maturation of neovasculatures in tumor tissues (*48*). Another recent study reported NGF treatment of mice implanted with DU145 prostate carcinoma cells induced innervation of perivascular nerves around tumor neovessels (*49*). NGF has also been shown to promote the development of new blood vessels (angiogenesis) through a direct interaction with α9β1 integrin (*50*). The mechanism involved in NGF effects on tumor growth needs further investigation.

3.1.2. *Involvement of NGF and p75NTR in apoptosis*

p75NTR expressed in cancer cells may act as a tumor suppressor when binding to NGF and negatively regulate cell growth and proliferation (*51*). Dimaras and Gallie have demonstrated that p75NTR suppressed the progression of both human and TAg-RB murine retinoblastoma (*52*). Medulloblastoma cells overexpressing p75NTR displayed a significant increase in apoptosis (*53*). Non-steroidal anti-inflammatory drugs which can induce p75NTR expression were also observed to induce apoptosis in prostate cancer cells (*54,55*).

Enforced p75NTR expression has been shown to inhibit gastric cancer growth *in vitro* and *in vivo* (*37*) by slowing cell cycle progression that results in cell accumulation of G0/G1 in prostate tumor cells (*56,57*) and bladder tumor cells (*58*). Moreover, p75NTR over-expression has been reported to induce mitochondria-mediated apoptosis through activation of a caspase-9/-7 cascade in human bladder tumor cells (*59*).

However, activation of the p75NTR by ligation with NGF leads to opposing effects in breast cancer. Binding of p75NTR with NGF has been shown to stimulate breast cancer cells survival signaling. The mechanism of this action is largely unknown but has been suggested to be mediated by activation of NF-κB signaling involving BEX2. Activation of the p75NTR receptor by NGF leads to diverse and sometimes opposing effects, in particular because of intracellular adaptor molecules and expression of co-receptors (*60,61*).

A study by Zhao *et al*. had shown that the gene silencing technique by siRNA targeting p75NTR was capable of inducing cancer cell apoptosis (*62*).

3.1.3. *Involvement of NGF and its receptors in metastasis*

Metastasis, the spread of cancer cells from the primary neoplasm to distant organs, is the most fearsome aspect of cancer (*63*). p75NTR has been shown to be a tumor suppressor of NGF-stimulated migration of human prostate tumor cells (*64*). Jin *et al*. showed that p75NTR expression inhibited the abilities of cell invasion and metastasis of gastric cancer cells *via* inhibiting the NF-κB signaling transduction (*65*). Overexpression of NGF has been shown to alter the blood vessel structure, leading to a reduction in vascular permeability and retention of cancer cells in the vasculature in lung carcinoma cells (*66*).

However, NGF has also been reported to promote prostate cancer cell metastasis, while intravenous gammaglobulin (IVIg), containing natural antibodies against NGF, is able to inhibit the migration of prostate cancer cell lines (*67*). On the other hand, TrkA overexpression promotes migration and invasion *in vitro* and enhances metastasis of xenografted breast cancer cells in immunodeficient mice (*68*). Further investigations are needed to elucidate the underlying mechanisms of these actions.

3.1.4. *Involvement of NGF and TrKA in cancer growth*

NGF/TrKA is involved in the regulating cell survival, differentiation, and proliferation, both in neuronal and non-neuronal cells (*69*). Recent studies demonstrated that TrkA expression was increased during the progression of medullary thyroid carcinoma and neuroblastoma (*70*).

Moreover, cancer cellular growth showed an association with NGF/TrkA in neuroblastomas and pancreatic cancer (*71,72*) and blocking the NGF/TrkA signal pathway can inhibit obviously tumor growth in prostate cancer (*73*). Besides, both *in vitro* and *in vivo* studies showed that TrkA stimulation can result in cellular growth in the breast cancer (*45,74*). TrkA appearing anti-apoptotic activities has a direct relationship with the presence of Ku70, which is the DNA repair protein and reported for its role in cell survival and carcinogenesis (*69*).

3.2. *Involvement of NGF and TrkA in cancer pain*

Pain is one of the most feared and burdensome symptoms in cancer patients and most individuals experience moderate to severe pain (*75-77*). Bone cancer pain is a high-risk of malignancies in patients with breast, prostate and lung cancer as these tumors have a remarkable ability to metastasize to bone (*78*).

NGF and its cognate TrkA receptor are believed to be a major mediator of chronic pain (*79*). NGF has been shown to be involved in perineural invasion (PNI), a process where cancer cells invade the surrounding nerves in pain generation in several malignancies, including breast, prostate and pancreatic cancers (*80*). Inhibiting the action of NGF/TrkA has been proposed to be a possible therapeutic approach to reduce PNI and block bone cancer pain (*81*).

NGF can promote the pathological reorganization of nearby TrkA sensory nerve fibers. The therapies of preventing this reorganization of sensory nerve fibers may provide insight into the mechanisms driving cancer pain (*82,83*). In a mouse model of prostate cancer-induced bone pain, both preemptive and late administration of monoclonal antibodies against NGF significantly reduced nociceptive behaviors, sensory and sympathetic nerve sprouting, and neuroma formation (*84*). Other studies showed that early/sustained, but not late/acute administration of a TrkA inhibitor ARRY-470 to mice markedly attenuated bone cancer pain and significantly blocked the ectopic sprouting of sensory nerve fibers and the formation of neuroma-like structures in the tumor bearing bone (*85*).

Both of these strategies carry its strength as well as limitations. For example, administration of monoclonal antibodies (anti-NGF or anti-TrkA) are generally selective than small inhibitors but carrying the risk of immune reactions. While small molecule inhibitors of TrkA, which are generally less expensive than monoclonal antibodies, allowing greater flexibility in dosing but generally less selective (*85*).

4. Discussion

NGF and its receptors are involved, directly or indirectly, in the pathogenesis of cancer and the manifesto of cancer pain through several mechanisms

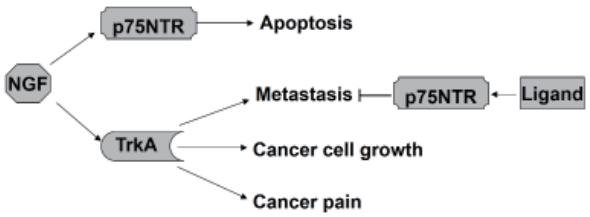

Figure 3. Effects of NGF and its receptors on tumorigenesis and cancer pain. "→" represents stimulatory modification; "⊣" represents inhibitory modification.

(Figure 3) such as inhibiting tumor growth, increasing apoptosis and promoting neuronal regulation of tumor blood flow. Future investigations will be provided for further insight into the actions of NGF and its receptors in cancer development and metastasis. Targeting the actions of NGF and its receptors may represent a potential direction for the treatment of tumorigenesis and cancer pain in future.

References

1. Lykissas MG, Batistatou AK, Charalabopoulos KA, Beris AE. The role of neurotrophins in axonal growth, guidance, and regeneration. Curr Neurovasc Res. 2007; 4:143-151.
2. Cui X, Chen L, Ren Y, Ji Y, Liu W, Liu J, Yan Q, Cheng L, Sun YE. Genetic modification of mesenchymal stem cells in spinal cord injury repair strategies. Biosci Trends. 2013; 7:202-208.
3. Wiesmann C, De Vos A. Nerve growth factor: structure and function. Cell Mol Life Sci. 2001; 58:748-759.
4. Mancino M, Ametller E, Gascón P, Almendro V. The neuronal influence on tumor progression. Biochim Biophys Acta. 2011; 1816:105-118.
5. Krüttgen A, Schneider I, Weis J. The dark side of the NGF family: Neurotrophins in neoplasias. Brain Pathol. 2006; 16:304-310.
6. Molloy NH, Read DE, Gorman AM. Nerve growth factor in cancer cell death and survival. Cancers. 2011; 3:510-530.
7. Levi-Montalcini R, Hamburger V. Selective growth stimulating effects of mouse sarcoma on the sensory and sympathetic nervous system of the chick embryo. J Exp Zool. 1951; 116:321-361.
8. Navis AR. Nerve Growth Factor. Embryo Project Encyclopedia. 2012; *http://hdl.handle.net/10776/1674*.
9. Aloe L. Rita Levi-Montalcini and the discovery of NGF, the first nerve cell growth factor. Arch Ital Biol. 2011; 149:175-181.
10. MacGrogan D, Saint-André JP, Dicou E. Expression of nerve growth factor and nerve growth factor receptor genes in human tissues and in prostatic adenocarcinoma cell lines. J Neurochem. 2006; 59:1381-1391.
11. Vanhecke E, Adriaenssens E, Verbeke S, Meignan S, Germain E, Berteaux N, Nurcombe V, Le Bourhis X, Hondermarck H. Brain-derived neurotrophic factor and neurotrophin-4/5 are expressed in breast cancer and can be targeted to inhibit tumor cell survival. Clin Cancer Res. 2011; 17:1741-1752.
12. Ullrich A, Gray A, Berman C, Dull TJ. Human β-nerve growth factor gene sequence highly homologous to that

of mouse. Nature. 1983; 303:821-825.
13. Varon S, Nomura J, Shooter E. The Isolation of the Mouse Nerve Growth Factor Protein in a High Molecular Weight Form. Biochemistry. 1967; 6:2202-2209.
14. Thoenen H, Barde Y. Physiology of nerve growth factor. Physiol Rev. 1980; 60:1284-1335.
15. Shi E, Wang B, Sun Q. Nerve growth factor and injured peripheral nerve regeneration. Neural Negen Res. 2008; 3:1273-1276.
16. Seidel MF, Herguijuela M, Forkert R, Otten U. Nerve growth factor in heumatic diseases. Semin Arthritis Rheum. 2010. 40:109-126.
17. Masoudi R, Ioannou MS, Coughlin MD, Pagadala P, Neet KE, Clewes O, Allen SJ, Dawbarn D, Fahnestock M. Biological activity of nerve growth factor precursor is dependent upon relative levels of its receptors. J Biol Chem. 2009; 284:18424-18433.
18. Johnson TV, Bull ND, Martin KR. Neurotrophic factor delivery as a protective treatment for glaucoma. Exp Eye Res. 2011; 93:196-203.
19. Haase G, Pettmann B, Raoul C, Henderson CE. Signaling by death receptors in the nervous system. Curr Opin Neurobiol. 2008; 18:284-291.
20. Hellebrand EE, Varbiro G. Development of mitochondrial permeability transition inhibitory agents: a novel drug target. Drug Discov Ther. 2010; 4:54-61
21. Arrighi N, Bodei S, Zani D, Simeone C, Cunico SC, Missale C, Spano P, Sigala S. Nerve growth factor signaling in prostate health and disease. Growth Factors. 2010; 28:191-201.
22. Huang CS, Zhou J, Feng AK, Lynch CC, Klumperman J, DeArmond SJ, Mobley WC. Nerve growth factor signaling in caveolae-like domains at the plasmamembrane. J Biol Chem. 1999; 274:36707-36714.
23. Iacaruso MF, Galli S, Martí M, Villalta JI, Estrin DA, Jares-Erijman EA, Pietrasanta LI. Structural Model for $p75^{NTR}$–TrkA Intracellular Domain Interaction: A Combined FRET and Bioinformatics Study. J Mol Biol. 2011; 414:681-698.
24. Barker P A. High affinity not in the vicinity?. Neuron. 2007; 53:1-4.
25. Matusica D, Skeldal S, Sykes AM, Palstra N, Sharma A, Coulson EJ. An Intracellular Domain Fragment of the p75 Neurotrophin Receptor ($p75^{NTR}$) Enhances Tropomyosin Receptor Kinase A (TrkA) Receptor Function. J Biol Chem. 2013; 288:11144-11154.
26. Nykjaer A, Willnow T E, Petersen C M. $p75^{NTR}$–live or let die. Curr Opin Neurobiol. 2005; 15:49-57.
27. Micera A, Lambiase A, Stampachiacchiere B, Bonini S, Bonini S, Levi-Schaffer F. Nerve growth factor and tissue repair remodeling: $trkA^{NGFR}$ and $p75^{NTR}$, two receptors one fate. Cytokine Growth Factor Rev. 2007; 18:245-256.
28. Cuello AC, Bruno MA, Allard S, Leon W, Iulita MF. Cholinergic involvement in Alzheimer's disease. A link with NGF maturation and degradation. J Mol Neurosci. 2010; 40:230-235.
29. Fahnestock M, Yu G, Michalski B, Mathew S, Colquhoun A, Ross GM, Coughlin MD. The nerve growth factor precursor proNGF exhibits neurotrophic activity but is less active than mature nerve growth factor. J Neurochem. 2004; 89:581-592.
30. Feng D, Kim T, Özkan E, Light M, Torkin R, Teng KK, Hempstead BL, Garcia KC. Molecular and structural insight into proNGF engagement of p75NTR and sortilin. J Mol Biol. 2010; 396:967-984.
31. Paoletti F, Covaceuszach S, Konarev PV, Gonfloni S, Malerba F, Schwarz E, Svergun DI, Cattaneo A, Lamba D. Intrinsic structural disorder of mouse proNGF. Proteins. 2009; 75:990-1009.
32. Paoletti F, Konarev PV, Covaceuszach S, Schwarz E, Cattaneo A, Lamba D, Svergun DI. Structural and functional properties of mouse proNGF. Biochem Soc Trans. 2006; 34:605-606.
33. Nykjaer A, Lee R, Teng KK, Jansen P, Madsen P, Nielsen MS, Jacobsen C, Kliemannel M, Schwarz E, Willnow TE. Sortilin is essential for proNGF-induced neuronal cell death. Nature. 2004; 427:843-848.
34. Nykjaer A, Willnow TE. Sortilin: a receptor to regulate neuronal viability and function. Trends Neurosci. 2012; 35:261-270.
35. Hermey G. The Vps10p-domain receptor family. Cell Mol Life Sci. 2009; 66:2677-2689.
36. Schweigreiter R. The dual nature of neurotrophins. Bioessays. 2006; 28:583-594.
37. Jin H, Pan Y, Zhao L, Zhai H, Li X, Sun L, He L, Chen Y, Hong L, Du Y. p75 neurotrophin receptor suppresses the proliferation of human gastric cancer cells. Neoplasia. 2007; 9:471-478.
38. Fahnestock M, Yu G, Coughlin MD. ProNGF: A neurotrophic or an apoptotic molecule?. Prog Brain Res. 2004; 146:101-110.
39. Cragnolini AB, Friedman WJ. The function of $p75^{NTR}$ in glia. Trends Neurosci. 2008; 31:99-104.
40. Bartkowska K, Turlejski K, Djavadian RL. Neurotrophins and their receptors in early development of the mammalian nervous system. Acta Neurobiol Exp (Wars). 2010; 70:454-467.
41. Skaper SD. The neurotrophin family of neurotrophic factors: An overview. Methods Mol Biol. 2012; 846:1-12.
42. Hondermarck H. Neurotrophins and their receptors in breast cancer. Cytokine Growth F R. 2012; 23:357-365.
43. Schecterson LC, Bothwell M. Neurotrophin receptors: old friends with new partners. Dev Neurobiol. 2010; 70:332-338.
44. Skaper SD. The neurotrophin family of neurotrophic factors: an overview. Methods Mol Biol. 2012; 846:1-12.
45. Nakagawara A. Trk receptor tyrosine kinases: A bridge between cancer and neural development. Cancer Lett. 2001; 169:107-114.
46. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144:646-674.
47. Chamary V, Robson T, Loizidou M, Boulos P, Burnstock G. Progressive loss of perivascular nerves adjacent tocolorectal cancer. Eur J Surg Oncol. 2000; 26:588-593.
48. Goda M, Atagi S, Amitani K, Hobara N, Kitamura Y, Kawasaki H. Nerve growth factor suppresses prostate tumor growth. J Pharmacol Sci. 2010; 112:463-466.
49. Sone Y, Ochi E, Matsuyama A, Fukuhara S, Goda M, Takatori S, Kawasaki H. Influence of nerve growth factor (NGF) on distribution of perivascular nerves in tumor neovasculatures of mouse corneal. Yakugaku zasshi. Journal of the Pharmaceutical Society of Japan. 2012; 132:157-160.
50. Walsh EM, Kim R, Del Valle L, Weaver M, Sheffield J, Lazarovici P, Marcinkiewicz C. Importance of interaction between nerve growth factor and α9β1 integrin in glial tumor angiogenesis. Neuro Oncol. 2012; 14:890-901.
51. Reis-Filho JS, Steele D, Di Palma S, Jones RL, Savage

K, James M, Milanezi F, Schmitt FC, Ashworth A. Distribution and significance of nerve growth factor receptor (NGFR/p75^{NTR}) in normal, benign and malignant breast tissue. Mod Pathol. 2006; 19:307-319.
52. Dimaras H, Gallie BL. The p75^{NTR} neurotrophin receptor is a tumor suppressor in human and murine retinoblastoma development. Int J Cancer. 2008; 122:2023-2029.
53. Küchler J, Hartmann W, Waha A, Koch A, Endl E, Wurst P, Kindler D, Mikeska T, Goodyer CG. p75^{NTR} induces apoptosis in medulloblastoma cells. Int J Cancer. 2010; 128:1804-1812.
54. Wynne S, Djakiew D. NSAID Inhibition of Prostate Cancer Cell Migration Is Mediated by Nag-1 Induction *via* the p38 MAPK-p75^{NTR} Pathway. Mol Cancer Res. 2010; 8:1656-1664.
55. Khwaja FS, Wynne S, Posey I, Djakiew D. 3, 3′-diindolylmethane induction of p75^{NTR}-dependent cell death *via* the p38 mitogen-activated protein kinase pathway in prostate cancer cells. Cancer Prev Res (Phila). 2009; 2:566-571.
56. Khwaja F, Tabassum A, Allen J, Djakiew D. The p75^{NTR} tumor suppressor induces cell cycle arrest facilitating caspase mediated apoptosis in prostate tumor cells. Biochem Biophys Res Commun. 2006; 341:1184-1192.
57. Krygier S, Djakiew D. The neurotrophin receptor p75NTR is a tumor suppressor in human prostate cancer. Anticancer Res. 2000; 21:3749-3755.
58. Khwaja F, Djakiew D. Inhibition of cell-cycle effectors of proliferation in bladder tumor epithelial cells by the p75^{NTR} tumor suppressor. Mol Carcinog. 2003; 36:153-160.
59. Tabassum A, Khwaja F, Djakiew D. The p75(NTR) tumor suppressor induces caspase-mediated apoptosis in bladder tumor cells. Int J Cancer. 2003; 105:47-52.
60. Naderi A, Teschendorff AE, Beigel J, Cariati M, Ellis IO, Brenton JD, Caldas C. BEX2 is overexpressed in a subset of primary breast cancers and mediates nerve growth factor/nuclear factor-κB inhibition of apoptosis in breast cancer cell lines. Cancer Res. 2007; 67:6725-6736.
61. Barker PA. p75NTR is positively promiscuous. novel partners and new insights. Neuron. 2004; 42:529-533.
62. Zhao Z, Jiang Z, Liu X, Chen Y, Jia W. Study on reversion of malignant phenotype of glioma by siRNA targeting p75 neurotrophin receptor. Zhonghua bing li xue za zhi. 2010; 39:400-404.
63. Fidler IJ. The pathogenesis of cancer metastasis. the 'seed and soil'hypothesis revisited. Nat Rev Cancer. 2003; 3:453-458.
64. Krygier S, Djakiew D. Neurotrophin receptor p75NTR suppresses growth and nerve growth factor-mediated metastasis of human prostate cancer cells. Int J Cancer. 2001; 98:1-7.
65. Jin H, Pan Y, He L, Zhai H, Li X, Zhao L, Sun L, Liu J, Hong L, Song J. p75 neurotrophin receptor inhibits invasion and metastasis of gastric cancer. Mol Cancer Res. 2007; 5:423-433.
66. Seidler K, Sydykov A, Müller-Brüsselbach S, Müller R, Weißmann N, Renz H, Nockher A. Nerve Growth Factor overexpression in Clara cells suppresses metastasis and tumor growth in a mouse model of experimental lung metastasis. Pneumologie. 2012; 66: A603.
67. Warrington RJ, Lewis KE. Natural antibodies against nerve growth factor inhibit *in vitro* prostate cancer cell metastasis. Cancer Immunol Immunother. 2011; 60:187-195.
68. Lagadec C, Meignan S, Adriaenssens E, Foveau B, Vanhecke E, Romon R, Toillon RA, Oxombre B, Hondermarck H, Le Bourhis X. TrkA overexpression enhances growth and metastasis of breast cancer cells. Oncogene. 2009; 28:1960-1970.
69. Com E, Lagadec C, Page A, El Yazidi-Belkoura I, Slomianny C, Spencer A, Hammache D, Rudkin BB, Hondermarck H. Nerve growth factor receptor TrkA signaling in breast cancer cells involves Ku70 to prevent apoptosis. Mol Cell Proteomics. 2007; 6:1842-1854.
70. McGregor LM, McCune BK, Graff JR, McDowell PR, Romans KE, Yancopoulos GD, Ball DW, Baylin SB, Nelkin BD. Roles of trk family neurotrophin receptors in medullary thyroid carcinoma development and progression. Proc Natl Acad Sci U S A. 1999; 96:4540-4545.
71. Brodeur GM, Minturn JE, Ho R, Simpson AM, Iyer R, Varela CR, Light JE, Kolla V, Evans AE. Trk receptor expression and inhibition in neuroblastomas. Clin Cancer Res. 2009; 15:3244-3250.
72. Zhu ZW, Friess H, Wang L, Bogardus T, Korc M, Kleeff J, Büchler MW. Nerve growth factor exerts differential effects on the growth of human pancreatic cancer cells. Clin Cancer Res. 2001; 7:105-112.
73. George DJ, Suzuki H, Bova GS, Isaacs JT. Mutational analysis of the TrkA gene in prostate cancer. Prostate. 1998; 36:172-180.
74. Lagadec C, Meignan S, Adriaenssens E, Foveau B, Vanhecke E, Romon R, Toillon RA, Oxombre B, Hondermarck H, Le Bourhis X. TrkA overexpression enhances growth and metastasis of breast cancer cells. Oncogene. 2009; 28:1960-1970.
75. Van den Beuken-van Everdingen MHJ, De Rijke JM, Kessels AG, Schouten HC, Van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol. 2007; 18:1437-1449.
76. Ahmedzai S. New approaches to pain control in patients with cancer. Eur J Cancer. 1997; 33:S8-S14.
77. Qi F, Li A, Inagaki Y, Gao J, Li J, Kokudo N, Li XK, Tang W. Chinese herbal medicines as adjuvant treatment during chemoor radio-therapy for cancer. Biosci Trends. 2010; 4:297-307.
78. Jimenez-Andrade JM, Mantyh WG, Bloom AP, Ferng AS, Geffre CP, Mantyh PW. Bone cancer pain. Annals of the New York Academy of Sciences. 2010; 1198:173-181.
79. Watson JJ, Allen SJ, Dawbarn D. Targeting nerve growth factor in pain: what is the therapeutic potential?. BioDrugs. 2008; 22:349-359.
80. Kolokythas A, Cox DP, Dekker N, Schmidt BL. Nerve growth factor and tyrosine kinase A receptor in oral squamous cell carcinoma: is there an association with perineural invasion?. J Oral Maxillofac Surg. 2010; 68:1290-1295.
81. Bapat AA, Hostetter G, Von Hoff DD, Han H. Perineural invasion and associated pain in pancreatic cancer. Nat Rev Cancer. 2011; 11:695-707.
82. Jimenez-Andrade JM, Bloom AP, Stake JI, Mantyh WG, Taylor RN, Freeman KT, Ghilardi JR, Kuskowski MA, Mantyh PW. Pathological sprouting of adult nociceptors in chronic prostate cancer-induced bone pain. J Neurosci. 2010; 30:14649-14656.

83. Mantyh WG, Jimenez-Andrade JM, Stake JI, Bloom AP, Kaczmarska MJ, Taylor RN, Freeman KT, Ghilardi JR, Kuskowski MA, Mantyh PW. Blockade of nerve sprouting and neuroma formation markedly attenuates the development of late stage cancer pain. Neuroscience. 2010; 171:588-598.
84. Jimenez-Andrade JM, Ghilardi JR, Castañeda-Corral G, Kuskowski MA, Mantyh PW. Preventive or late administration of anti-NGF therapy attenuates tumor-induced nerve sprouting, neuroma formation, and cancer pain. Pain. 2011; 152:2564-2574.
85. Ghilardi JR, Freeman KT, Jimenez-Andrade JM, Mantyh WG, Bloom AP, Kuskowski MA, Mantyh PW. Administration of a tropomyosin receptor kinase inhibitor attenuates sarcoma-induced nerve sprouting, neuroma formation and bone cancer pain. Mol Pain. 2010; 6:87.

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