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Review

Nerve growth factor & TrkA as novel therapeutic targets in cancer

Ihsan Ekin Demir *, Elke Tieftrunk, Stephan Schorn, Helmut Friess, Güralp O. Ceyhan

Department of Surgery, Klinikum rechts der Isar, Technische Universität München, 81675 Munich, Germany

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ABSTRACT

In the past 20 years, nerve growth factor (NGF) and its receptors TrkA & p75NTR were recognized to be overexpressed in the overwhelming majority of human solid cancers. Recent studies discovered the presence of overactive TrkA signaling due to TrkA rearrangements or TrkA fusion products in frequent cancers like colorectal cancer, thyroid cancer, or acute myeloid leukemia. Thus, targeting TrkA/NGF via selective small-molecule-inhibitors or antibodies has gained enormous attention in the drug discovery sector. Clinical studies on the anti-cancer impact of NGF-blocking antibodies are likely to be accelerated after the recent removal of clinical holds on these agents by regulatory authorities. Based on these current developments, the present review provides not only a broad overview of the biological effects of NGF-TrkA-p75NTR on cancer cells and their microenvironment, but also explains why NGF and its receptors are going to evoke major interest as promising therapeutic anti-cancer targets in the coming decade.

Contents

1. Introduction

Nerve growth factor (NGF) is a trophic factor that promotes the survival of sensory and sympathetic neurons in vitro and in vivo. Indeed, denervation of peripheral organs leads to diminished NGF secretion from the periphery and results in hypoplasia of the corresponding sensory and sympathetic ganglia. Although the presence of such a vital factor for neuronal survival was recognized earlier, the actual discovery of NGF by Rita Levi-Montalcini around the middle of the 20th century was possible in in vitro bioasays in which pronounced neurite outgrowth from chicken embryo neuronal tissue was observed when it was placed next to mouse sarcoma tissue pieces. These pioneering experiments indirectly showed that not only peripheral tissues, but especially neoplastic tissues are rich sources of NGF. NGF continues to be a fascinating

* Corresponding author at: Department of Surgery, Klinikum rechts der Isar, Technische Universität München, Ismaninger Str. 22, D-81675 München, Germany.
E-mail address: ekin.demir@tum.de (I.E. Demir).

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biomolecule with multiple crucial effects during a multitude of biological processes and diseases, including neurodegenerative disorders, neuro-inflammatory disorders like multiple sclerosis; neuropsychiatric diseases like Alzheimer's disease, schizophrenia, depression, bipolar disorder; chronic neuropathic pain encountered e.g. in arthritis; or in cardiovascular disorders. Yet in harmony with the first seminal experiments that led to its discovery, NGF has been subject to intensive investigation by numerous research groups that focused on its effects in cancer. Collectively, all these studies could demonstrate highly relevant biological effects of NGF during cancers of varying origin, related to cancer generation, progression, prognosis, signaling in cancer cells, cancer microenvironment, cancer-associated neuroplasticity, and cancer-associated pain. The current review provides an overview of the so far reported biological and clinical effects of NGF in experimental and human cancer.

1.1. NGF signaling: the key aspects

NGF belongs to the family of neurotrophins that also include brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 [1]. It consists of two 13-kDa beta strands that twist around each other and connect via disulfide bonds within a prototypical cystine knot, and is usually encountered as a dimer [2,3]. The effects of NGF are mediated upon its binding to one of its two receptors: 1) the tropomysoine receptor kinase A (TrkA), which is the high-affinity NGF receptor and a transmembrane tyrosine kinase, and 2) the p75 neurotrophin receptor (p75NTR), which is the low-affinity NGF receptor and belongs to the tumor necrosis factor receptor (TNF receptor) superfamily, and was the first TNF receptor superfamily member to be characterized [4].

Upon binding of NGF, TrkA dimerizes and auto-phosphorylates the tyrosine residues at the cytoplasmic tails [5] (Fig. 1). These phosphorylated sites then enable the docking and phosphorylation of adaptor proteins from the cytoplasm, including the Shc, growth factor-receptor bound protein-2 (Grb2), and Gbr2-associated Binder-1 (GAB1) [6]. These proteins either activate 1) the phosphatidylinositol-3 kinase (PI3K) and 2) Akt kinase [4,7]. Alternatively, the TrkA phosphorylation results in recruitment of a guanine nucleotide exchange factor (GEF) that allows GTP phosphorylation and activation of the membrane-associated G protein Ras [4,8]. Activated Ras in turn phosphorylated Raf that then activates the mitogen-activated protein kinase (MAPK) and subsequently the ribosomal s6 kinase (RSK) [4,8]. The activation of Akt or RSK results in phosphorylation of the cyclic AMP response element binding protein (CREB) transcription factor that then translocates into the nucleus and mediates the trophic and anti-apoptotic effects of NGF [4,9]. When there is deficiency of NGF, the Akt or MAPK pathways cannot suppress the activity of cell death-promoting transcription factors such as c-Jun, resulting in apoptosis [10,11] (Fig. 1).

On the other hand, signaling via p75NTR can have contrasting effects in a cell. Upon binding of NGF or its uncleaved precursor pro-NGF, recruited cytoplasmic adaptor proteins recruit the tumor necrosis factor receptor member TRAF6 [12], which can in turn activate the inhibitor of the kappaB kinase (IKK) and thus the canonical NFkappaB signaling. RelA/p65 in the NFkappaB pathway acts as regulator of nuclear gene transcription and primarily promotes cell survival [13]. Alternatively, TRAF6 and neurotrophin receptor interacting factor (NRIF) can activate c-Jun N-terminal kinase (JNK) [14,15], which phosphorylates the transcription factor c-Jun. Activated c-Jun subsequently mediates apoptosis by upregulating the expression of pro-apoptotic genes [15].

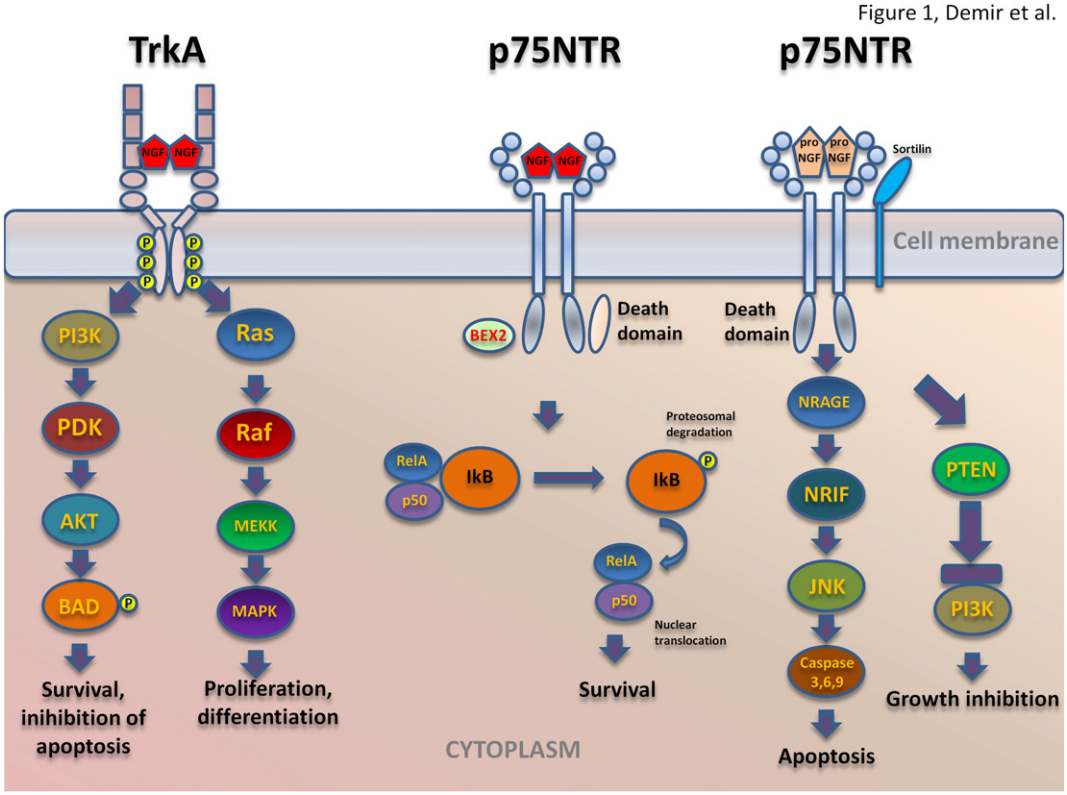

Fig. 1. *Overview of the intracellular pathways that are linked to NGF, TrkA and p75NTR-mediated signaling. Left*: Binding of mature NGF dimmers to TrkA leads to phosphorylation TrkA and can subsequently activate survival and proliferative pathways via activation of PI3K-Akt or Ras-MAPK. *Middle*: The binding of mature NGF dimers to p75NTR exerts a similar pro-survival effect via phosphorylation and proteasomal degradation of inhibitor of kappa B (IkappaB) and subsequent translocation of transcription-activating RelA/p50 dimers into the nucleus. *Right*: p75NTR can, though, also be activated by the uncleaved pro-NGF together with simultaneous recruitment of the co-receptor sortilin. This association launches the interaction of the MAGE protein NRAGE with the cytosolic domain of p75NTR. p75NTR mediates the activation of the pro-apoptotic JNK pathway. Furthermore, p75NTR can also activate PTEN (phosphatase and tensin homolog deleted on chromosome 10) and inhibit the PI3K-activation due to Trk activity, overall resulting in the inhibition of Trk-mediated pro-growth effects. Please refer to the section on "NGF signaling: the key aspects" in the manuscript for the corresponding references.