The Neurotrophins and Neuropoietic Cytokines: Two Families of Growth Factors Acting on Neural and Hematopoietic Cells

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ABSTRACT: Recent progress has revealed similarities between the receptors and signaling systems used by neurotrophic factors as compared to other growth factors and cytokines. The neurotrophins use a family of receptor tyrosine kinases known as the Trk receptors, whereas ciliary neurotrophic factor (CNTF) uses a "cytokine receptor" system that shares receptor components with a number of distantly related cytokines. We have used a human embryonal carcinoma cell line and human leukemia cell lines to examine the actions of the neurotrophins and CNTF on cellular differentiation. Our findings demonstrate that specific combinations of neurotrophic factors are required to influence the neuronal progenitor cells to become postmitotic mature CNS neurons. Such synergistic interactions may play an important role in modulating the differentiation of a wide assortment of neuronal precursors in the developing nervous system. Furthermore, our studies with leukemia cells suggest that neurotrophic factors may play a similar role in hematopoietic differentiation and that these factors may have therapeutic application in leukemia differentiation.

Although neurotrophic factors represent a group of ligands that were originally identified for their ability to support neuronal survival, several of these factors can also exert unique actions on cells outside of the nervous system, including those of the immune system. The first family of neurotrophic factors is collectively known as the "neurotrophins" and comprises several members that are related to nerve growth factor (NGF). The second family is represented by ciliary neurotrophic factor (CNTF), a neuropoietic cytokine that is distantly related to a number of hematopoietic cytokines. The receptors used by these two families of neurotrophic factors can be classified as either "receptor tyrosine kinases" or "cytokine receptors." Both the receptors and signaling systems that mediate the actions of the neurotrophic factors are similar to those used by other growth factors.[1,2] The neurotrophins use a family of receptor tyrosine kinases, known as the Trks, which are similar to the receptor tyrosine kinases used by traditional growth factors such as platelet-derived growth factor (PDGF). On the other hand, CNTF utilizes a multicomponent "cytokine receptor" system, which includes a specificity-conferring α-receptor component acting in concert with signal-transducing β-receptor components that are shared with its distant cytokine relatives.

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The distinct signaling pathways activated by different classes of neurotrophic factors can collaborate and exert synergistic effects on target cells. For example, the CNTF family of cytokines together with the NGF family of growth factors can act in concert to influence the neuronal differentiation program.[3] The collaborative effects elicited by treatment with multiple neurotrophic factors are dramatically different from the effects of individual factors. These synergistic interactions may play an important role in modulating the differentiation of neuronal precursors during embryonic development.

THE RECEPTORS FOR THE NEUROTROPHINS

Five members of the neurotrophin family have thus far been isolated, with nerve growth factor (NGF) being the prototype for this family.[4] The other members include brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4, alternatively neurotrophin-5 or NT4/5), and neurotrophin-6 (NT-6). The mammalian counterpart for NT-6 has yet to be identified.

The actions of the neurotrophins on target cells are mediated by the Trk family of receptor tyrosine kinases, which are activated by ligand-induced dimerization. The three known Trk receptors display overlapping specificities for the neurotrophins. A large body of evidence indicates that NGF is the ligand specific for the TrkA receptor, BDNF and NT-4/5 are the preferred ligands for the TrkB receptor, and NT-3 primarily acts on the TrkC receptor, although it can also activate the TrkB receptor in certain cell types.[4,5]

EFFECTS OF THE NEUROTROPHINS ON NEURONAL CELLS

The actions of the neurotrophins are predominantly specific to neuronal cells due to the relatively restrictive distributions of the Trk receptors. In addition to regulating neuronal survival, neurotrophic factors can exert other actions that are important for the differentiation and maintenance of the nervous system. A variety of *in vitro* and *in vivo* studies have revealed the actions of these factors on both overlapping and discrete neuronal populations. The recent use of gene-targeting technology to generate mice that lack the individual neurotrophin or Trk receptors not only confirms the actions of the neurotrophins previously observed, but also reveals new target sites for the neurotrophins.[2,6]

Numerous *in vitro* studies as well as recent studies of the neurotrophin mutant mice reveal that each of the neurotrophins are critical for the survival of different populations of peripheral neurons.[2,7] For example, both *in vitro* studies and analysis of mice lacking either NT3 or its cognate receptor TrkC demonstrated that NT-3 is a specific survival factor for large proprioceptive neurons found in the dorsal root ganglion.[2] In the case of BDNF and NT-4, the *in vitro* actions of these two neurotrophins are quite similar, as they both can activate TrkB.[8] Whereas the BDNF mutant mice die within the first few weeks of life, however, the NT-4 mutant mice are long-lived.[9] Intriguingly, this is apparently accounted for by the dependence of a subpopulation of the nodose-petrosal ganglia on BDNF and not NT-4. Furthermore, a subpopulation of

sympathetic and nodose/petrosal neurons appears to require more than one neurotrophin. It is likely that sequential actions of the neurotrophins are required during development.

Although there have been numerous reports on the survival and differentiating actions of the neurotrophins on cultured CNS neurons, analysis of neurotrophin and Trk mutants thus far reveals relatively few deficits within the CNS. For example, the cholinergic neurons in the basal forebrain as well as dopaminergic and retinal ganglion neurons are not notably affected in mice lacking NGF or BDNF or their cognate receptors.[9,10] It is possible that the effects of the neurotrophins in the CNS are more subtle partly due to the fact that CNS neurons receive more redundant trophic support through their elaborate synaptic connections.

EFFECTS OF THE NEUROTROPHINS ON CELLS OF THE IMMUNE SYSTEM

In addition to their well-documented neurotrophic effects, the spectrum of action of the neurotrophic factors can be extended to cells outside of the nervous system, as exemplified by the presence of their receptors in the hematopoietic and immune systems.[11,12] Increasing evidence has suggested that neurotrophic factors may be involved in the process of hematopoiesis such as promoting colony growth and differentiation of myeloid progenitor cells.[11,13,14]

As part of an effort to delineate the roles of neurotrophic factors in hematopoiesis, we have recently undertaken a systematic study on the expression of neurotrophic factors and their receptors in various leukemia cell lines.[15] Our findings demonstrate the expression of NGF, NT-3, and NT-4/5 mRNA in leukemia cells, consistent with a possible involvement of these neurotrophins in the differentiation of hematopoietic cells. Furthermore, retinoic acid induced the expression of TrkA, the high-affinity receptor for NGF in several leukemia cell lines, raising the possibility that NGF and TrkA may work in an autocrine manner in these cells. Interestingly, previous observations have demonstrated that NGF stimulated colony growth of myeloid progenitor cells and that NGF promoted the differentiation of hematopoietic progenitor cells, granulocytes, and basophil/mast cells *in vitro*.[11,13,14]

It has been suggested that NGF may be able to form a modulatory loop with cytokines. For example, the expression of IL-6 was enhanced by NGF in thymic stromal cell cultures, while IL-2 and NGF increased the expression of the receptor for each other in B lymphocytes.[16,17] It is conceivable that one growth factor may trans-regulate the expression of other growth factors and/or receptors in these leukemia cell lines. Furthermore, synergistic effects of NGF and cytokines have also been observed. For example, NGF can synergize with granulocyte–macrophage colony-stimulating factor (GM-CSF) to stimulate human basophil differentiation and can also synergize with macrophage colony-stimulating factor (M-CSF) to stimulate colony formation of hematopoietic progenitor cells *in vitro*.[13,14] Combinatory and sequential actions of these growth factors may be required for the initiation, progression, and maturation of retinoic acid-induced differentiation of leukemia cells, in a manner analogous to the normal hematopoiesis process.

RECEPTOR COMPLEX FOR THE CILIARY NEUROTROPHIC FACTOR

Originally identified on the basis of its ability to support survival of ciliary neurons, CNTF is now known for its broad spectrum of actions on a variety of neuronal populations in the nervous system. A major breakthrough in understanding how CNTF initiates signaling on target cells came with the initial identification and cloning of a CNTF-binding protein, designated CNTFRα.[18] This protein was found to exhibit sequence homology of CNTFRα with IL6Rα, one of the receptor components used by a hematopoietic cytokine, interleukin-6 (IL-6). Binding of IL-6 to IL6Rα results in the recruitment of a second receptor component, gp130, to initiate signaling.[19] A theoretical analysis also reveals that CNTF is in fact a member of a superfamily of hematopoietic cytokines and shares structural homologies with IL6, leukemia inhibitory factor (LIF), granulocyte colony–stimulating factor (G-CSF), and oncostatin M.[20] Some of these cytokines can mimic CNTF with respect to its actions on cells of the nervous system, but also display a broad array of actions outside of the nervous system.

The homology between CNTFRα and IL6Rα, together with the lack of a cytoplasmic domain in CNTFRα, raised the possibility that CNTF might require a second receptor component to initiate intracellular signaling, similar to the signal transducer gp130 used by IL6. Subsequent studies reveal that CNTF shares its signaling receptor components with its distantly related cytokines, such as LIF and IL6.[21–23] Thus, while the LIF receptor complex comprises gp130 and LIFRβ, which was initially cloned as a LIF-binding protein, CNTF requires a third receptor component, CNTFRα. The finding that the tripartite CNTF receptor complex includes within it the bipartite LIF receptor accounts for the parallel actions of CNTF and LIF on many neuronal cells. Thus, the neuronal specificity of CNTF can be explained by the restricted expression of the CNTF receptor α component, while the broad actions of LIF outside the nervous system are due to the widespread distributions of its receptor components, gp130 and LIFRβ.[24] It is the specific expression of CNTFRα that underlies the role of CNTF as a neurotrophic factor and that distinguishes CNTF from its more generally acting cytokine relatives. Taken together, the structural homologies for CNTF and its related cytokines as well as their shared receptors have provided an unexpected link between the nervous system and the immune system (FIG. 1).

Unlike the Trk receptors or other receptor tyrosine kinases, the tripartite receptor components for CNTF lack intrinsic kinase domains. Subsequent studies demonstrated the crucial involvement of a family of cytoplasmic tyrosine kinases, Jak/Tyk, in initiating signal transduction subsequent to ligand stimulation. The known members of this nonreceptor kinase family are crucial in the signaling pathways for several cytokines, such as interferon α, interferon γ, and erythropoietin. Unlike other cytokines, which activate only a certain subset of the Jak/Tyk kinases, the CNTF-related cytokines are unique in being capable of activating all the known members of the Jak/Tyk family of kinases.[25]

REGULATION OF CNTF AND CNTFRα EXPRESSION AFTER NERVE INJURY

A large body of evidence indicates that CNTF may play an important role in the injury response in the nervous system. Dramatic changes in the level of

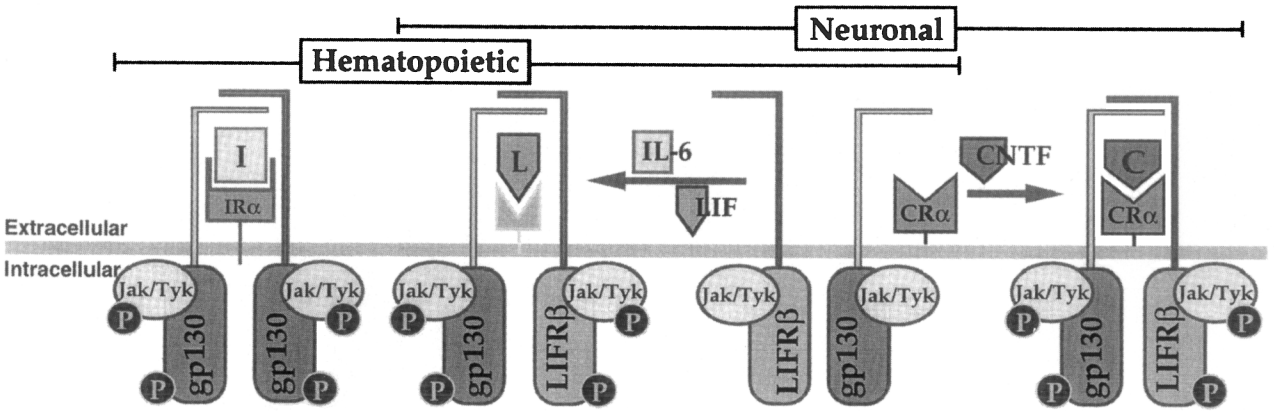

FIGURE 1. Schematic diagram of receptor complexes utilized by CNTF (C), LIF (L), and IL6. Ligand binding induces dimerization of the β-signaling subunits, that is, heterodimerization of LIFRβ and gp130 in the case of CNTF and LIF and homodimerization of gp130 for IL6. Activation of the nonreceptor tyrosine kinases (Jak/Tyk) that are pre-associated with the β components mediates the subsequent signaling events. Addition of CNTFRα (CRα), which is predominantly found in the nervous system, converts a functional LIF receptor into a functional CNTF receptor complex. The actions of CNTF are largely restricted to the nervous system, while LIF has widespread actions (both neuronal and hematopoietic).

expression of both CNTF and its receptor CNTFRα occur following neural trauma in the CNS or PNS. For example, mechanical lesions in the brain resulted in a dramatic increase in CNTF bordering the wound site, being localized to reactive astrocytes in the resulting glial scar.[26-28] It is possible that CNTF may act not only as a trophic factor for damaged neurons as expected, but may also act on astrocytes at the sites of injury.[29] Thus, the responses of these cells to CNTF may participate in the recovery process following injury.

We have demonstrated that a soluble form of CNTFRα can form a heterodimeric complex with CNTF to activate signaling in cells that express only the two β components (gp130 and LIFRβ) and normally respond only to LIF but not CNTF. Similarly, CNTF-related cytokines such as IL6 may be able to elicit responses from nonresponsive neuronal cells via its soluble receptor. For example, we have observed that addition of IL6 together with IL6Rα to sympathetic neurons or PC12 cells result in phosphorylation of gp130, the β-signaling component (Ip and Wong, unpublished observations). Thus, the availability of soluble α receptor components may trigger responsiveness from cells that are normally nonresponsive. Peripheral nerve injury such as the transection of the sciatic nerve results in a dramatic increase in CNTFRα in skeletal muscle.[30] It is indeed an intriguing possibility that soluble CNTFRα released from skeletal muscle together with CNTF released from the nerve might collaborate and act on diverse cell types (such as blood-derived monocytes) at the site of injury that normally do not respond to CNTF due to the absence of CNTFRα. Such interaction might play an important role in the regeneration response following injury. However, recent studies from our laboratory have unexpectedly demonstrated that the upregulation of CNTFRα observed in denervated rat skeletal muscle was not detected in chick skeletal muscle following injury.[31,32] Studies are in progress to delineate the mechanism underlying the differential regulation of CNTFRα in rat and chick skeletal muscle after nerve injury.

EFFECTS OF CNTF ON NEURONAL CELLS

Early studies have identified CNTF as a trophic factor that supports the survival of parasympathetic neurons from embryonic chick ciliary ganglion neurons.[33,34] It is now well established that a wide variety of peripheral and central neurons also respond to CNTF.[35,36] For example, CNTF supports the survival of sensory neurons and preganglionic sympathetic spinal cord neurons, as well as induces the cholinergic differentiation of sympathetic neurons. This is consistent with the restrictive expression of CNTFRα to neural tissues, including all known peripheral targets of CNTF, such as sympathetic, sensory, and parasympathetic ganglia.[24]

Prominent expression of CNTFRα in various parts of the motor system predicts a unique role for CNTF in maintaining motor system function. In addition to its survival and differentiative effects on cultured motor neurons *in vitro*, CNTF can also rescue axotomized motor neurons.[37,38] Retrogradely transported CNTF appears to be important in the regenerative response of neuronal cells following axotomy. In the CNS, CNTF has been shown to increase the survival of cultured hippocampal neurons while degeneration of specific neuronal population in the CNS could be prevented in the presence of CNTF.[39,40] The broad expression of CNTFRα throughout the central nervous system predicts the existence of additional potential targets for CNTF action.

EFFECTS OF CNTF ON NEURONAL PRECURSOR CELLS

Cytokines of the CNTF family, such as IL-6 and LIF, have been shown to affect various lineages of hematopoiesis.[41] Based on the prominent expression of CNTF by early neuronal progenitor cells, CNTF may play a key signaling role during neuropoiesis in a manner similar to its cytokine relatives during hematopoiesis. In fact, CNTF can act on even earlier precursors, including those that are responsive to LIF. Embryonic stem cells, for example, express a functional CNTF receptor complex, and CNTF can maintain the pluripotentiality of these cells in a manner similar to that observed with LIF.[42] Similarly, CNTF has been demonstrated to exert trophic actions on embryonal carcinoma P19 cells.[43] It has been demonstrated that CNTF induces the survival as well as differentiation of P19 cells toward a neuronal phenotype. Because P19 cells also respond to retinoic acid, which also induces cellular differentiation in these cells, work is in progress in our laboratory to examine possible interactions between the signaling pathways activated by CNTF and retinoic acid.

Parallel actions on cells of the sympathoadrenal lineage can similarly be elicited by both CNTF and LIF. These two neuropoietic cytokines have been demonstrated to induce cholinergic function and influence neuropeptide expression in sympathetic neurons and their precursors, as well as inhibit the proliferation of sympathetic precursors. We have used a CNTF-responsive sympathoadrenal precursor cell line, MAH, to explore a potential role for CNTF in the development of sympathetic neurons. CNTF or LIF was found to interact synergistically with FGF and NGF in the generation of NGF-dependent postmitotic neurons.[3] Similarly, CNTF and FGF exert differentiative effects on primary chromaffin cells that are distinct from those induced by either factor alone. Recent observations from our laboratory also support a similar role for CNTF in the differentiation of human embryonal carcinoma cells into CNS neurons (Cheung, Fu and Ip, unpublished observations).

TARGETED GENE DISRUPTIONS FOR CNTF AND CNTFRα

Despite the impressive effects of exogenously provided CNTF on embryonic and adult neuronal populations, recent analyses of mice and humans containing mutated CNTF genes suggest that CNTF does not appear to play a critical role in the development of motor neurons or other neuronal populations. Mice lacking CNTF appear remarkably normal and display only mild motor neuron problems without major neurological abnormalities.[44] Interestingly, a significant proportion (2.5%) of the Japanese population are homozygous for a null mutation of CNTF and yet appear quite normal even in old age.[45] Taken together, these findings suggest that CNTF is not critical during development and may only play an important role during instances of nerve trauma.

In contrast to the findings with mice lacking CNTF, mice lacking CNTFRα die shortly after birth and exhibit profound deficits in all motor neuron populations examined.[46] Thus, the observed discrepancy between the phenotype resulting from the lack of CNTF as compared with the phenotype resulting from the lack of CNTFRα strongly predicts that there exists another alternative ligand for CNTFRα. This alternative ligand for CNTFRα may play a more critical role than CNTF during early development. The identity of this ligand that

shares the CNTFRα as predicted from the genetic evidence, however, remains to be determined.

CONCLUSION

The neurotrophins and CNTF are classic examples of neurotrophic factors that are well known for their neurotrophic actions on neuronal cells. Such unique properties of the neurotrophic factors are primarily because of the relatively restrictive expression of their receptor systems to the nervous system. However, increasing evidence has now demonstrated that these neurotrophic factors also have the ability to affect cells of the immune system. In the case of CNTF, the similarities in both the ligand structure and receptor structure with its distantly related cytokines also provide an unexpected link between the nervous system and immune system. Indeed, many parallels can be drawn between the process of neuropoiesis and hematopoiesis. Multiple classes of neurotrophic factors may exist so that they can signal collaboratively to act on neuronal procursor cells, much like the striking synergies observed among various cytokines during the process of hematopoiesis. Thus, although the precise factors involved may differ in various lineages, the general principle that multiple factors interact synergistically and sequentially in the generation of neuronal diversity is likely to be widespread during neuronal development.

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