Selective Regulation of TrkA and TrkB Receptors by Retinoic Acid and Interferon-γ in Human Neuroblastoma Cell Lines*

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Trk receptors are a family of genes implicated in the survival, differentiation, and growth of certain neurons and tumors of the nervous system. A better understanding of the regulation of Trk receptors is relevant for developmental and oncolgical studies. Human neuroblastoma (NB) cell lines constitutively express low levels of TrkA mRNA, while TrkB mRNA is not readily detectable. Differentiation of NB cells is accompanied by a differential modulation of Trk expression in human NB cells. Nanomolar concentrations of RA induce a stable increase of TrkB mRNA. A transient induction of TrkA mRNA levels requires micromolar concentrations of RA. Induction of both TrkA and TrkB mRNA does not require new protein synthesis. However, RA-induced TrkB mRNA expression is transcriptionally regulated, while the transient RA-induced increase of TrkA mRNA is a consequence of extended mRNA stability. Interferon-γ (IFN-γ) selectively increases TrkA mRNA without affecting TrkB mRNA levels. Similar to RA, IFN-γ does not modify the transcriptional rate of TrkA mRNA, but rather increases TrkA mRNA stability. Thus, RA and IFN-γ differentially regulate TrkA or TrkB expression in the same cell type by predominantly transcriptional (TrkB) or posttranscriptional (TrkA) mechanisms. Such experiments indicate the complexity of Trk mRNA regulation and also indicate compounds that may affect neurotrophin responsiveness in developing neural cells.

The Trk family of tyrosine kinase receptors plays a crucial role in neuronal survival, differentiation, function, and target organ innervation during development (Snider et al., 1994). Although originally described as an oncogene (Martin-Zanca et al., 1986), the Trk gene product has been recently identified as the high affinity receptor for nerve growth factor (NGF)1 (Kaplan et al., 1991a; Klein et al., 1991a). The Trk gene family includes at least three members (TrkA, TrkB, and TrkC) that are structurally and functionally related (Barbacid et al., 1991). Their interactions with neurotrophins are complex; NGF interacts with TrkA, BDNF binds TrkB, NT-3 binds TrkC and (to a lesser extent) TrkA and TrkB, while NT4/5 binds TrkB and (to a limited extent) TrkA (Kaplan et al., 1991b; Soppet et al., 1991; Klein et al., 1991a, 1991b; Squinto et al., 1991; Lambelle et al., 1991; Glass et al., 1991; Berkemeier et al., 1991; Ip et al., 1992; Tsoufas et al., 1993).

Despite the significance of the Trks to the development of the nervous system, little is known about the mechanisms by which these genes are regulated. In situ hybridization studies show that the expression of Trk mRNAs increase during embryonal life yet decreases in most tissues after birth (Klein et al., 1990b; Martin-Zanca et al., 1990; Masana et al., 1993). The observation that the survival dependence of trigeminal neurons switches from BDNF to NT3 or NGF during development implies that specific neural populations may also change their pattern of Trk receptors expression (Buchman et al., 1993; Verdi et al., 1994). Such studies indicate that a complex set of environmental signals must be coordinated to regulate Trk expression. Therefore a critical issue toward understanding the development of neuronal cells is to determine the mechanisms that control Trk expression.

Neurotrophins regulate the expression of their specifc receptors, as well as other Trk family members. NGF induces TrkB mRNA in astrocytes (Kumar et al., 1993) and TrkA mRNA in the basal forebrain and in PC12 cells (Holtzman et al., 1992). NT-3 induces TrkA in proliferating neuroblasts (Verdi et al., 1994). Increased intracellular cAMP levels induce TrkB in astrocytes (Kumar et al., 1993) and TrkA in the immortalized sympathoadrenal MAH cell line (Birren et al., 1992). In retinal cells, the steady-state levels of TrkB and TrkC mRNAs increase upon exposure to light and decrease in the dark (Okazawa et al., 1994). IFN-γ recently has been shown to be able to increase TrkA mRNA levels in NB cell lines (Shikata et al., 1994). Members of the nuclear hormone receptor family also modulate expression of Trk receptors. Estrogen increases TrkA mRNA expression in primary sensory neurons (Sohrabji et al., 1994), while a thyroid hormone receptor transfected into the mouse N2 cell line increases TrkB and decreases TrkA and TrkC mRNA levels (Pastor et al., 1994). RA modulates expression of TrkA receptors in immature chick sympathetic neurons (Rodriguez-Tebar et al., 1991). Furthermore, RA induces neurite extension in human NB cells expressing BDNF via induction of TRK B mRNA and p145TrkB expression (Kaplan et al., 1993).

The variety of compounds capable of altering Trk expression indicates that diverse signal transduction pathways regulate Trk gene expression. Retinoids play a key role during normal morphogenesis of the developing chick limb (Wagner et al., 1990) and are being viewed with increasing importance in the nervous system since retinoid deprivation during embryogenesis causes central nervous system damage in the chick (Krishnamurthy et al., 1963). Sites of RA synthesis have been noted in the spinal cord (McCaffery et al., 1994a), in the basal fore-
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brain (McCaffrey et al., 1994b), and in the retina (McCaffrey et al., 1993), and RA increases neuron survival and axon out-growth in spinal cord cultures (McCaffery et al., 1994b). IFNs are well known to be a key element of the host defense against viruses and tumors. IFNs regulate the expression of several genes at either the transcriptional or post-transcriptional levels, such as the 2–5A synthetase that induce cell resistance to viruses, and interleukins that control growth and differentiation of many types of cells (Villcek et al., 1994). Although IFN-γ is typically produced by T lymphocytes and natural killer cells, sensory neurons have been shown to produce an interferon-like molecule called N-IFN-γ (Olsson et al., 1994). N-IFN-γ has similar activities to lymphocyte derived IFN-γ, in that it can control myoblast proliferation, as well as regulate induction of major histocompatibility complex antigens in muscle and macrophage culture cells (Olsson et al., 1994).

In this report we use human NB cells as a model system to study the molecular mechanisms regulating Trk genes expression in an in vitro differentiation model (Kaplan et al., 1993). We examine TrkA and TrkB gene regulation in both the presence and absence of RA or IFN-γ and describe distinct mechanisms of regulation of these genes.

EXPERIMENTAL PROCEDURES

Cell Culture—The NB cell lines SMS-KCN (KCNR) (Reynolds et al., 1986) and NGBP (Schwab et al., 1986) were cultured as described previously (Thiele et al., 1985). Cells were treated with indicated concentrations of all-trans-retinoic acid (Sigma), IFN-α and IFN-γ (Collaborative Biomedical Research, Bedford, MA) at 1000 units/ml, or control solvent for the indicated times. In some experiments, cells were treated with 5 μg/ml actinomycin D (Sigma) to block mRNA synthesis, or 5 μg/ml cycloheximide (Sigma) to block protein synthesis in NB cells (Thiele et al., 1988).

RNA Analysis—RNA isolations and hybridizations were performed as described previously (Thiele et al., 1985; Thiele et al., 1988). Twenty-five micrograms of total RNA were analyzed as described previously (Thiele et al., 1985) and hybridized with [32P]-labeled insert DNA isolated from plasmids containing rat TrkB (Middlemas et al., 1991; Klein et al., 1990b), human TrkA (Martin-Zanca et al., 1989), or GAPDH. Washing conditions were as described (Thiele et al., 1985). Membranes were exposed to X-Omat AR film at –70 °C using a Lightning Plus intensifying screen.

In Vitro Transcription Analysis—Nuclear run-on assay was performed as described previously (Gaetano et al., 1991).

Protein Analysis—Cells were exposed to IFN-γ or control solvent and then treated for 5 min with 100 ng/ml NGF (Upstate Biotechnology Inc., Lake Placid, NY). Cells were lysed, and the lysates immunoprecipitated as described previously (Kaplan et al., 1991a, 1991b). After washing with cold Tris-buffered saline, cells (1 × 10⁶) were lysed in 1 ml of 1% Nonidet P-40 lysis buffer (20 mM Tris pH 8.0, 150 mM NaCl, 10% glycerol, 1 mM phenylmethylsulfonyl fluoride, aprotinin (0.15 unit/ml), 20 μM leupeptin, and 1 mM sodium vanadate) at 4 °C for 20 min. Insoluble material was removed by centrifugation at 4 °C for 10 min at 10,000 × g. The lysates were immunoprecipitated with anti-pan Trk 203 (Hempestad et al., 1992). Immunoprecipitations were described as described previously (Kaplan et al., 1993). Protein blots were probed overnight at 4 °C with anti-Trk(P) antibody 4G10 (provided by Morrison NC1-FCRDC). Blots were analyzed using an ECL chemiluminescence system (Amersham Corp.).

RESULTS

Kinetics of Trk mRNA Expression in RA-treated KCNR Cells—Previous studies indicated that RA increased TrkB but not TrkA mRNA expression in KCNR NB cells when evaluated at 8 days (Kaplan et al., 1993). In order to determine the kinetics of RA-induced TrkA and TrkB mRNA expression, the NB cell line KCNR was treated with 5 μM RA or control solvent and TrkA and TrkB mRNA expression was evaluated after 3, 6, and 9 days of treatment. The results indicated that KCNR constitutively expressed TrkA mRNA in control cells and densitometric analysis indicated that the basal level of expression increased with time in culture (Fig. 1A). RA treatment of KCNR cells transiently stimulated TrkA mRNA expression causing a 2.1-fold increase of TrkA mRNA levels at 3 days. At later time points TrkA mRNA expression progressively decreased, reaching control levels by day 9. In contrast to TrkA, only a faint TrkB mRNA signal was detectable in control cells, indicating that KCNR cells constitutively express very low level of TrkB mRNA in control cells. RA treatment, however, induced a 12-fold increase in TrkB mRNA at 3 days that reached 34-fold after 6 days and thereafter remained relatively stable (Fig. 1A). To determine how early RA-induced TrkA mRNA expression occurred, KCNR cells were treated for 3, 6, and 12 h with 5 μM RA or control solvent. A 1.7-fold induction of TrkA mRNA was detectable after 3 h (Fig. 1B), which reached 3-fold after 12 h of RA treatment. A 2.5-fold increase in TrkB mRNA was also detectable as early as 3 h after RA treatment and increased thereafter. The kinetics of expression suggest differential regulation of TrkA and TrkB mRNA after RA treatment.

During development, gradients of RA exist in tissues that have been postulated to influence morphogenesis (Hunter et al., 1991). Previously, we determined that nanomolar concentrations of RA induced TrkB mRNA, yet TrkA levels were relatively unaffected at 8 days (Kaplan et al., 1993). Since the increase in TrkA levels occurred within hours of RA treatment, KCNR cells were treated for 24 h with different concentrations of RA. Increases in TrkB mRNA were detectable only in cells treated with higher RA concentrations (5 μM RA) (Fig. 1C). The apparent increase in TrkA mRNA in pigcromal RA-treated cells was due to overloading of this lane, as indicated by densitometric analysis of TrkA mRNA levels normalized to GAPDH mRNA levels. In contrast, TrkB mRNA expression was induced by nanomolar RA (Fig. 1C). These results indicate that micro-molar concentrations of RA are necessary to induce TrkB mRNA, whereas nanomolar concentrations are required to induce TrkA mRNA.

Regulation of Trk mRNA by RA—Steady-state mRNA levels are influenced by the rate of gene transcription and/or by the stability of the mRNA transcripts. To evaluate the mechanisms by which RA regulates Trk gene expression, the stability of Trk mRNA was determined in RA-treated and control cells. KCNR

![Figure 1](http://www.jbc.org/Downloaded from http://www.jbc.org/).
cells were treated for 48 h with 5 μM RA or control solvent. After 2 days, actinomycin D (5 μg/ml) was added to the cultures for up to 5 h to inhibit new mRNA synthesis. In control cells TrkA mRNA half-life was approximately 4 h (Fig. 2B), while in RA-treated cells TrkA mRNA levels remained unchanged even at 5 h. Stability of TrkB mRNA in control cells could not be determined since levels were below detection. In RA-treated cells, TrkB mRNA levels were unchanged even after 5 h (Fig. 2A). These results indicate that RA treatment increases the stability of TrkA mRNA. Since TrkB mRNA was not detectable in control cells, it was not possible from these studies to evaluate whether RA influences TrkB mRNA stability. However, RA-induced TrkB mRNA levels were unaffected even after 5 h.

The early induction of Trk mRNA by RA suggests that RA may also directly regulate Trk gene transcription. To evaluate this hypothesis, nuclei were isolated from two different NB cell lines, KCNR and NGP. Previous studies indicated that RA induces Trk mRNA in NGP (Lucarelli et al., 1994). Both cell lines were treated for 2 days with 5 μM RA and gene transcription assessed by nuclear run-on assays. TrkA mRNA transcription was not significantly altered in nuclei from RA-treated cells, compared to nuclei from control cells in either cell line (Fig. 2C). However, TrkB mRNA transcription was increased 2- and 27-fold in nuclei from RA-treated KCNR and NGP cells compared to controls, respectively. These data indicate that in both the KCNR and NGP cell lines, RA stimulates TrkB but not TrkA gene transcription.

To verify whether RA-induced Trk gene expression requires de novo protein synthesis, KCNR cells were treated with RA or control solvent in the presence or absence of cycloheximide.
(CHX, 5 μg/ml), which inhibits 99% of protein synthesis (Thiele et al., 1988). RA-induced TrkA or TrkB mRNA expression occurred in the presence of CHX, indicating that de novo protein synthesis was not required to mediate RA induction of TrkA or TrkB mRNA (Fig. 2D). In the presence of CHX, TrkA and TrkB mRNA levels increased above those detected in the absence of CHX. This indicates that basal steady-state Trk mRNA levels may be affected by short-lived proteins.

Regulation of Trk mRNA Expression in IFN-treated KCNR Cells—Interferons, as well as retinoids, have antiproliferative and differentiative activities in NB cells. To evaluate whether IFN-α and IFN-γ altered Trk mRNA expression in NB cells, KCNR cells were treated for 3 days with RA, IFN-α, and IFN-γ alone or in combination. IFN-γ, but not IFN-α, stimulated a 2.2-fold increase in Trk mRNA levels (Fig. 3A). TrkA mRNA induction in IFN-γ-treated cells was similar to that observed with RA-treated cells, and treatment with both agents showed additive effects on the level of TrkA mRNA expression. Neither IFN-α or IFN-γ significantly increased TrkB mRNA expression. To assess whether the increase in TrkA mRNA was an early response to IFN-γ treatment, KCNR cells were treated with IFN-γ for 6 and 24 h, and TrkA mRNA levels were determined by Northern blot analysis (Fig. 3B). IFN-γ modestly (1.3-fold) increased TrkA mRNA levels after 6 h of treatment, and a 2-fold increase was detectable after 24 h of treatment (Fig. 3C).

Regulation of TrkA mRNA by IFN-γ—IFN-γ is known to stimulate gene transcription. To evaluate whether IFN-γ transcriptionally regulates TrkA gene expression, expression levels were assessed by nuclear run-on assay after treatment of KCNR cells with IFN-γ or control solvent. Similar to the changes observed in RA-treated cells, no changes in TrkA transcription rate could be detected in IFN-γ-treated cells (Fig. 4C). In order to study whether new protein synthesis is required for the IFN-γ-mediated increases in TrkA mRNA expression, KCNR cells were incubated for 24 h with IFN-γ or control solvent and treated for the last 6 h with CHX or control solvent. IFN-γ stimulated an increase in TrkA mRNA expression in the presence of CHX (Fig. 4D), indicating that new protein synthesis was not required by IFN-γ to mediate the induction of TrkA mRNA. Furthermore, the combination of IFN-γ and CHX resulted in a greater increase in TrkA mRNA expression (13-fold) than in cells treated with IFN-γ (3.8-fold) or CHX (2-fold) alone.

To evaluate whether IFN-γ could influence TrkA mRNA stability, cells were treated for 3 days with IFN-γ or control solvent and incubated for 2 and 4 h in the presence of 5 μg/ml actinomycin D to inhibit new mRNA synthesis. In control cells the half-life of TrkA mRNA was approximately 3 h (Fig. 4B). In contrast, TrkA mRNA in IFN-γ-treated cells was stable for a period longer than 4 h (Fig. 4A). The estimated half-life of TrkA mRNA in control cells, calculated in Figs. 2B and 4B, is consistently and clearly shorter than the half-life of TrkA mRNA in RA- and IFN-γ-treated cells. These results suggest that the increase in the mRNA steady-state levels is primarily mediated by an increase in the stability of TrkA mRNA.

TrkA Receptor Autophosphorylation in RA- and IFN-γ-treated Cells—To evaluate whether RA and IFN-γ induced an increase in functional TrkA receptors, cells were incubated in the presence of RA, IFN-γ, or control solvent, and after 3 days cultures were stimulated with NGF for 5 min. Cell lysates were immunoprecipitated with an anti-pan Trk antibody, resolved by polyacrylamide gel electrophoresis analysis, blotted, and probed with an anti-Tyr(P) antibody to assess ligand-induced tyrosine phosphorylation of the receptor (Fig. 5). In cells incubated with the control solvent the phosphorylated TrkA receptor was observed only in NGF-treated cells, indicating that KCNR cells expressed a functional TrkA receptor. In RA-treated KCNR cells there was a 3-fold increase in the intensity of the anti-Tyr(P) signal, while IFN-γ treatment caused a 5-fold increase, indicating an increase in p140TrkA that is consistent with the RA and IFN-γ induced increase in TrkA mRNA. The levels of TrkA protein were below the levels of detection to be observed by TrkA-specific antibodies (not shown).

**DISCUSSION**

This study details the mechanisms of Trk gene regulation in NB cells and shows that the changes in the steady-state levels
of TrkA and TrkB mRNA are mediated via distinct mechanisms of gene regulation. Although Trk genes play a key role in the development and function of the nervous system, there has been little analysis of the molecular mechanisms by which these genes are regulated. Our studies indicate that TrkA mRNA is constitutively expressed in NB cells and RA induces a transient increase in the steady-state mRNA levels that is primarily mediated by an increase in mRNA stability. In contrast, the basal level of TrkB mRNA is typically below the levels detected by Northern blot analysis. However, RA induces a sustained increase in TrkB mRNA that is accompanied by an increase in TrkB mRNA transcription. Furthermore, IFN-γ increases TrkA, but not TrkB mRNA levels. TrkA mRNA induction by either IFN-γ or RA is principally mediated by increasing TrkA mRNA stability.

A direct role of RA on TrkB gene transcription is supported by experiments showing that RA induces an increase in TrkB mRNA transcription and by studies indicating that the increase in steady-state TrkB mRNA levels occurs within a few hours of treatment and in the absence of de novo protein synthesis. In KCNR cells, there is only a 2-fold increase in TrkB mRNA transcription at 3 days, while TrkB mRNA steady-state levels are increased 12-fold increase over controls at similar time. Although we were not able to evaluate whether the stability of TrkB mRNA was increased by RA, the difference in transcriptional increase and the steady-state levels would indicate that RA may also enhance TrkB mRNA stability. In contrast to the regulation of TrkB, increases in TrkA mRNA stability may be the major determinant for the increase in the steady-state TrkA mRNA levels. However, similar to the regulation of TrkB, RA mRNA levels increase after a few hours of RA treatment in the absence of de novo protein synthesis. Thus, it is possible that RA mediates an increase in TrkA transcription, although it is below the level of sensitivity of nuclear run-on assays. Treatment of NB cells with CHX results in increases in TrkA and TrkB mRNA steady state. This result suggests that short lived proteins negatively regulate TrkA and TrkB mRNA and may affect either mRNA stability, or regulate mRNA transcription. Distinct concentrations of RA regulate Trk gene expression; 10^{-5} \text{M} RA is required to induce TrkA mRNA, whereas 1000-fold less (10^{-6} \text{M} RA) induces TrkB mRNA. The observation that concentrations of RA in the embryonic retina that express high levels of TrkB (Jelsma et al., 1993) are approximately 500 nM (McCaffery et al., 1993) provides physiologic support to our finding that nanomolar concentrations of RA induce TrkB mRNA in vitro. Retinoid signal transduction is mediated by two types of nuclear receptors, retinoic acid receptor and retinoic X receptor, that bind specific sequences (RARE) in the promoter of genes such as the RAR-β (de The et al., 1990) and homeobox genes (Wang et al., 1985). Experiments on the hu-
man Hox B homebox gene have shown that the interactions between RA and the retinoid receptors are complex and concentration-related, since RA concentrations ranging from 100 nM to 100 pM activate different gene clusters (Simeone et al., 1990). Extension of these studies to RA-regulated Trk gene expression suggests that expression of Trk genes are selectively dependent on RA concentration. Although the presence of RARE in the promoter region of TrkA and TrkB is still not known, our results would support the hypothesis that a RARE exists in the TrkB promoter, although we cannot exclude the possibility that a RARE also exists in the TrkA promoter. However, it is also possible that the increase in TrkA stimulated by RA is not a direct effect, but rather a consequence of the ability of micromolar, but not nanomolar, concentrations of RA to arrest NB cell growth (Matsumoto et al., 1995). Increases in NGF responsiveness have been noted in another NB cell model in which proliferation was arrested by aphidicolin, a drug that inhibits DNA polymerase (LoPresti et al., 1992), as well as in aphidicolin-treated proliferating neuroblastoma from embryonic sympathetic ganglia (Verdi et al., 1994). Delineation of the molecular mechanism by which RA may affect transcription of Trk genes awaits characterization of the promoters of these two genes.

The present study provides the first analysis of the mechanism of regulation of TrkA by IFN in neuronal cells. IFN-γ has been shown to regulate the expression of many genes in the immune system at either the transcriptional or post-transcriptional level. Our evidence indicates that, similar to RA, IFN-γ regulates TrkA mRNA primarily by a post-transcriptional mechanism. Determination of TrkA mRNA stability indicates that TrkA mRNA decays at a slower rate in IFN-γ-treated cells compared to control. Furthermore, we do not detect any changes in TrkA mRNA transcription in nuclear run-on experiments. These data are similar to studies in which IFN-γ has been shown to post transcriptionally regulate an increase in Interleukin-8 mRNA in human monocytes (Bosco et al., 1994), and a decrease in c-fos mRNA in macrophages (Radzioch et al., 1991). A role for IFN-γ in the nervous system development has not been identified; however, IFN-γ-mediated induction of TrkA may be an important step for enhancement of neural cell survival during periods of immune cell activation.

Differential expression of TrkA and TrkB is well documented in the nervous system, and the ability to switch receptor phenotype is inferred from studies documenting changes in neuronal responses to selective neurotrophins (Birren et al., 1994). NB tumors are derived from cells in the embryonal neural crest destined to be sympathetic ganglia or chromaffin cells. NB tumors have been shown to express distinct patterns of Trk receptors as well (Nakagawara et al., 1993; Nakagawara et al., 1994). NB tumors in patients with a good prognosis express relatively high levels of TrkA (Nakagawara et al., 1992), while many of those who have a poor prognosis have tumors that express BDNF and TrkB mRNA (Nakagawara et al., 1994). It is possible that NB tumors arise from cells at different stages of differentiation or from distinct neural crest cell lineages. Aside from being a prognostic marker, differential Trk expression may contribute to the variable prognosis of patients with NB tumors. Recently, we have found that activation of the BDNF-TrkB signal transduction pathway stimulates NB cell invasion, a property of metastatic NB cells, while activation of the NGF-TrkA signal transduction pathway may inhibit cell invasion (Matsumoto et al., 1995). When a cell line derived from a poor prognosis patient produces high levels of TrkA by gene transfection, treatment with NGF arrests cell growth (Matsushima et al., 1993). These studies indicate that the biology of a tumor from a poor prognosis patient may be altered by high levels of TrkA expression. Although we find that IFN-γ stimulates a 2-fold increase in TrkA autophosphorylation in NB cell lines in vitro, it is not clear whether this increase is sufficient to alter cell growth and differentiation. Current studies are aimed at defining factors that can induce a high level of TrkA expression in NB cells, by either increasing TrkA transcription or mRNA stability.

Acknowledgments—We thank Fabrizio Ensoli for the helpful comments on the manuscript, Priscilla Sassoli de Bianchi and Shirley Johnson for technical assistance, and J eff Hughes and Staci Canion for editorial assistance.

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