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REVIEW

Neurotrophins and the immune system

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Abstract

The neurotrophins are a family of polypeptide growth factors that are essential for the development and maintenance of the vertebrate nervous system. In recent years, data have emerged indicating that neurotrophins could have a broader role than their name might suggest. In particular, the putative role of NGF and its receptor TrkA in immune system homeostasis has become a much studied topic, whereas information on the other neurotrophins is scarce in this regard. This paper reviews what is known about the expression and possible functions of neurotrophins and their receptors in different immune tissues and cells, as well as recent data obtained from studies of transgenic mice in our laboratory. Results from studies to date support the idea that neurotrophins may regulate some immune functions. They also play an important role in the development of the thymus and in the survival of thymocytes.

Key words immunocompetent cells; lymphoid organs; neurotrophins; $p75^{NTR}$; Trk receptors.

Introduction

Half a century ago, a polypeptide that induced neuronal growth was discovered and named nerve growth factor (NGF) (Levi-Montalcini, 1952). Several decades later, a series of other molecules with similar structure and functions were identified, and together they form a family of polypeptide growth factors called the neurotrophins (NTs). Besides NGF, this family comprises brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and NT-4/5, all of which are present in all tetrapods, except NT-4/5, which has not been found in birds (Hallböök, 1999). In teleosts, two additional neurotrophins closely related to NGF, namely NT-6 and NT-7, have been identified (Götz et al. 1994; Lai et al. 1998; Nilsson et al. 1998). NTs probably originated from the duplication of an ancestral gene, which gave rise to two intermediate genes that then produced NGF and NT-3, and BDNF and NT-4/5, respectively (Hallböök, 1999).

NTs bind to two kinds of receptors with dissociation constants of 10^{-9} M and 10^{-11} M that denominate low- and high-affinity receptors, respectively (for references see Lewin & Barde, 1996; Friedman & Greene, 1999). The low-affinity receptor is $p75^{NTR}$. It belongs to the tumour necrosis factor receptor superfamily, and serves as a pan-neurotrophin receptor (Rodríguez-Tebar et al. 1990, 1992; Hempstead, 2002). The $p75^{NTR}$ locus produces two proteins, a full-length protein and a short variant lacking a segment of the extracellular domain (Dechant & Barde, 1997; von Schack et al. 2001). The functional role of $p75^{NTR}$ has not yet been fully elucidated (Bothwell, 1996; Lee et al. 2001; Roux & Barker, 2002). It is assumed to function as a co-receptor for the high-affinity receptors (for references see Esposito et al. 2001; Roux & Barker, 2002) and as a mediator of the pro-apoptotic programmes induced by NGF depending on the physiological or developmental stage of the cells (Carter & Lewin, 1997; Casaccia-Bonnefil et al. 1998; Kuner & Hertel, 1998; Meldolesi et al. 2000; Miller & Kaplan, 2001; Chao & Bothwell, 2002; Kendal et al. 2002). Moreover, it mediates the migration of

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Schwann cells (Bentley & Lee, 2000), and is involved in cell fate decisions in some non-nervous cells such as macrophages (Caroleo et al. 2001) and vascular smooth muscle cells (Wang et al. 2001). $p75^{NTR}$ also interacts with proteins that promote mitotic cycle arrest, thereby mediating a role of NTs in the cell cycle (Lopez-Sanchez & Frade, 2002).

The protein tyrosine kinase Trk receptors TrkA (gp140*trk*A), TrkB (gp145*trk*B) and TrkC (gp145*trk*C) act as specific, high-affinity neurotrophin receptors (Meakin & Shooter, 1992; Glass & Yancopoulos, 1993; Barbacid, 1995; Lewin & Barde, 1996; Huang & Reichardt, 2001). These Trk receptors have an extracellular domain, which binds the different neurotrophins, and a cytosolic domain whose tyrosine-kinase activity is essential for signal transduction. Variants of Trks with insertions in either the extracellular domain or the tyrosine kinase domain have been identified for TrkA (Barker et al. 1993; Shelton et al. 1995) and TrkC (Lamballe et al. 1993; Valenzuela et al. 1993; Shelton et al. 1995). In addition, truncated receptors lacking the kinase domain have been described for TrkB and TrkC, but not for TrkA (Middelmas et al. 1991; Valenzuela et al. 1993; Tsoulfas et al. 1996). Variants of the extracellular domain of TrkA have also been detected in certain tissues (Dubus et al. 2000). Each member of the Trk family shows preferential ligand bindings among neurotrophins (Ip et al. 1993). TrkA is the preferred receptor for NGF (Kaplan et al. 1991; Klein et al. 1991), but has a lower efficiency for NT-3 or NT4/5 binding. TrkB is bound by BDNF and NT-4 and, to a lesser extent, by NT-3 (Klein et al. 1991; Ip et al. 1992). TrkC has a unique ligand, NT-3 (Lamballe et al. 1991) (Fig. 1).

As occurs with NTs, the genes codifying for the Trk receptors probably also originate from a common ancestral gene (van Kesteren et al. 1998; Hallböök, 1999). Thus both neurotrophins and Trk receptors are present in all vertebrates and their sequences are highly conserved during phylogeny.

The actions of NTs in the nervous system have been well studied and extensively reviewed (Fariñas, 1999; Huang & Reichardt, 2001), although the concept that the role of NTs is confined to cells of the nervous system is being reconsidered (Tessarollo, 1998). Thus detailed

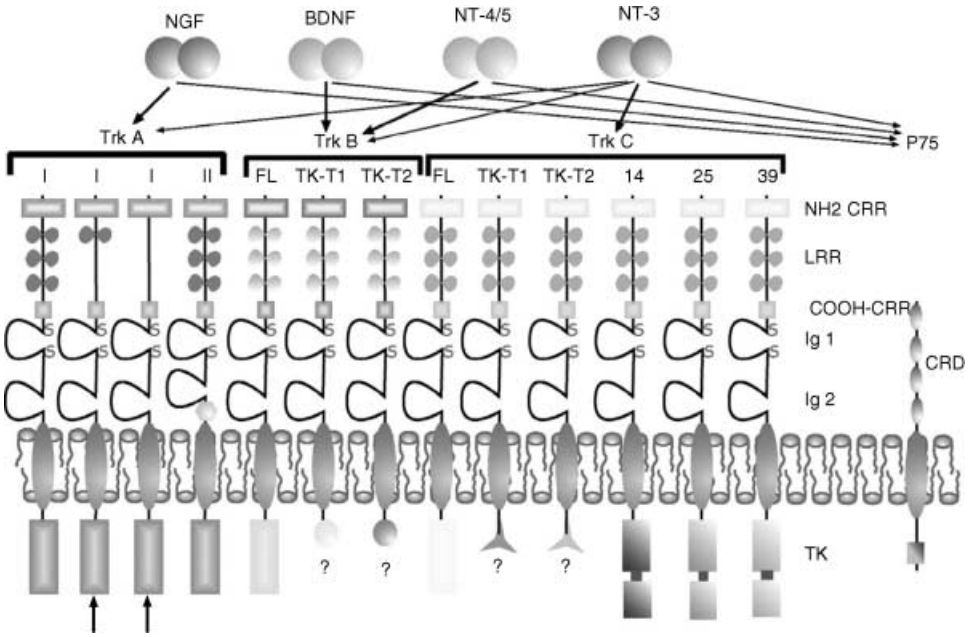

Fig. 1 Schematic representation of the structure of Trk and $p75^{NTR}$ neurotrophin receptors, and of the neurotrophins that bind each of them: thick arrows represent the primary receptor–ligand pairing; thin arrows indicate other binding possibilities. Two different isoforms of TrkA have been isolated, and termed TrkAI and TrkAII. Three TrkAI isoforms are known (shown at the left of the figure). In the thymus, two specific TrkAI isoforms have been isolated (arrows at bottom left), which show total or partial deletion of amino cysteine-rich regions of the extracellular domain. TrkAII differs from TrkAI in that it carries a small insertion of six amino acids next to the transmembrane domain (hexagon). With regard to TrkB and TrkC, full-length (FL), tyrosine kinase truncated (TK-T1 and TK-T2), and tyrosine kinase inserted (14, 25 and 39, equivalent to the number of amino acids forming the insertion) isoforms have been isolated. NH2 CRR, amino cysteine-rich regions; COOH-CRR, carboxy cysteine-rich regions; CRD, cysteine-rich domains; LRR, leukine-rich region; TK, tyrosine kinase domain.

Table 1 Localization of neurotrophin receptors in lymphoid organs of vertebrates

Tissue	TrkA	TrkB	TrkC	p75
Bone marrow	Erythroblasts[1]	Erythroblasts[1] Neutrophils[1] Megacariocytes[1] Haematopoietic cells[2]	Megacariocytes[1] Promyelocytes[1]	Dendritic cells[2,4]
Thymus	Dendritic cells[5,6,7] Epithelial cells[2,5,6,7] Thymocytes[2]	Macrophages[8] Dendritic cells[9,10]	Stromal cells[9,10]	Dendritic cells[7] Epithelial cells[5,11,12,13]
Bursa of Fabricius	Epithelial cells[9,14]	Dendritic cells[14]	Epithelial cells[14]	
Spleen		Macrophages[2,15]	Stromal cells[10]	Follicular dendritic cells[6] Lymphocytes[2]
Lymphoid nodes	Dendritic cells[5,16]	Dendritic cells[16] Macrophages[2]		Dendritic cells[6] Lymphocytes[17]
Peyer's patches	Dendritic cells[18] Epithelial cells[18]	Macrophages[18]		
Palatine tonsils	Dendritic cells[6,19] Epithelial cells[6,19]	Macrophages[19]	Interdigitating dendritic cells[19]	Dendritic cells[6]
Cecal tonsil	Epithelial cells[20]	Macrophages[20] Dendritic cells [20]	Macrophages[20] Dendritic cells[20]	

[1]Labouyrie et al. (1999); [2]Shibayama & Koizumi (1996); [3]Cattoretti et al. (1993); [4]Caneva et al. (1995); [5]Hannestad et al. (1997); [6]Labouyrie et al. (1997); [7]Parrens et al. (1998); [8]García-Suárez et al. (1998); [9]Ciriaco et al. (1996); [10]Hannestad et al. (2000); [11]Pescarmona et al. (1993); [12]García-Suárez et al. (2000b); [13]García-Suárez et al. (2001); [14]Ciriaco et al. (1997); [15]Pérez-Pérez et al. (1999); [16]García-Suárez et al. (1997); [17]Chesa et al. (1988); [18]Levanti et al. (1997); [19]Hannestad et al. (1995); [20]Hannestad et al. (1998).

studies have revealed significant actions of neurotrophins in a wide variety of tissues outside the nervous system, especially in the immune system (Otten & Gadient, 1995; Tessarollo, 1998; Aloe et al. 1999; Aloe, 2001; Sariola, 2001).

It is now well established that NGF is involved in the normal pattern of sympathetic innervation of the lymphoid organs (Kannan et al. 1994, 1996), because they concentrate NGF conveyed by the lymphoid vessels from the sources (Carlson et al. 1995, 1998). However, other functions of NTs in the lymphoid organs are less clear. The aim of this review is to compile and discuss current data about the occurrence and distribution of NTs and their receptors in the lymphoid organs and immunocompetent cells, focusing on the possible functional significance of these molecules as modulators of the immune system in health and disease.

Presence of the neurotrophins and their receptors in the immune system (Table 1)

Detailed studies carried out during the last decade about the tissue distribution and cellular localization of NT receptors have revealed they are present in cell subpopulations of primary and secondary lymphoid organs, as well as in some kinds of immunocompetent cells (see Aloe et al. 1999). Therefore, both these tissues and cells are potential targets for NTs. Interestingly, in all vertebrate species examined, from humans to fishes, NTs and/or their receptors have been detected in lymphoid organs (Ciriaco et al. 1996; Hannestad et al. 1997, 2000). Recently, a major contribution to understanding the *in vivo* functions of NTs has been provided by the study of the phenotype of mice lacking NTs or functional NT receptors (García-Suárez et al. 2000a, 2002; Ruberti et al. 2000).

Thymus

In the thymus, mRNAs for all NTs and their receptors have been detected (Timmusk et al. 1993; Laurenzi et al. 1994; Lomen-Hoerth & Shooter, 1995; Labouyrie et al. 1997; Parrens et al. 1998). Nevertheless, identification of the cells expressing each of them has not yet been fully accomplished, and it has still not been proved whether or not mechanisms of autocrinia or paracrinia exist within the organ.

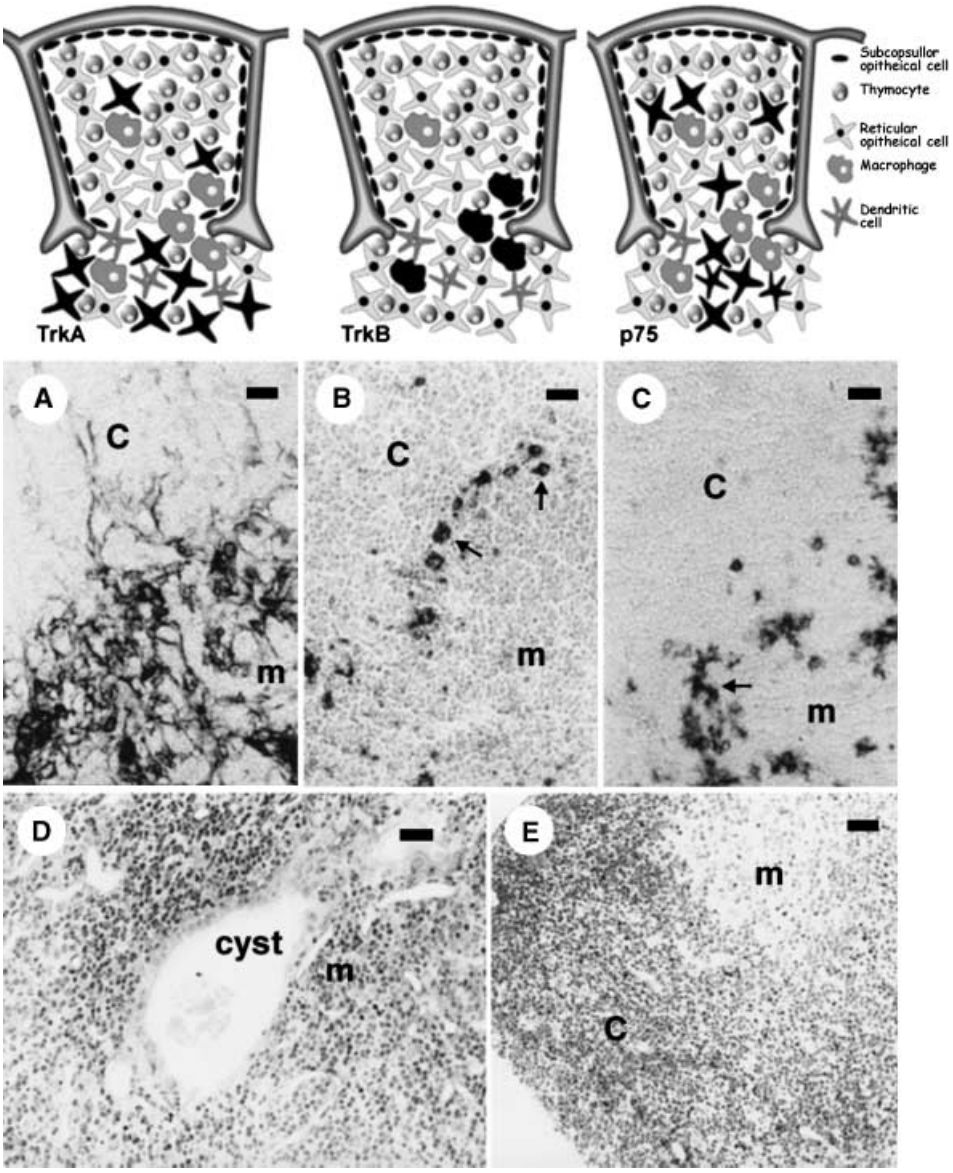

Fig. 2 The upper pictures illustrate the localization of TrkA-(left), TrkB-(middle) and $p75^{NTR}$ (right)-positive cells in the rodent thymus; receptor-expressing cells are represented in black. Below are shown the corresponding TrkA (A), TrkB (B) and $p75^{NTR}$ (C) immunostained sections. The cells expressing TrkA are subcapsular and medullar thymic epithelial cells (mouse); those showing TrkB immunoreactivity, concentrated at the cortico-medullary border (arrows), are macrophages (rat), and $p75^{NTR}$ immunoreactivity is confined to a subpopulation of medullar thymic epithelial cells (arrows, rat). The lower images correspond to morphological aspects of functionally trkA- and trkB-deficient mice. The *trkA*-kinase –/– mouse thymus (D) is characterized by disorganization of the thymic architecture and the presence of medullar endodermic cysts containing amorphous material and cell debris, whereas the *trkB*-kinase –/– mouse (E) shows images of apoptotic lymphocyte death, especially in the cortex. c, cortical; m, medullar. Scale bar = 5 μm.

In mammals, TrkA is mainly localized in subcapsular and medullar epithelial cells (Shibayama & Koizumi, 1996; Hannestad et al. 1997; Labouyrie et al. 1997; Parrens et al. 1998, 1999; García-Suárez et al. 2000b, 2001; Yoon et al. 2003), but is not expressed by thymocytes (Maroder et al. 1996; Hannestad et al. 1997; Labouyrie et al. 1997; Parrens et al. 1999; Levanti et al. 2001) (Fig. 2). The thymic TrkA seems to be functional as NGF administration produces epithelial cell hypertrophy *in vivo* (Abramchik et al. 1988) and increases IL-6 transcription in epithelial cells *in vitro* (Screpanti et al. 1992). Recently, Dubus et al. (2000) identified thymus-specific TrkA variants lacking leucine-rich motifs of the extracellular domain, which have been implicated in

modulating NGF binding (Fig. 1). Interestingly, in malignant thymic epithelial cell tumours the expression of TrkA is lost (Parrens et al. 1998), and $p75^{NTR}$ is expressed (Parrens et al. 1999). Furthermore, during thymus regeneration of the rat thymus following acute-induced involution of the organ, the expression of TrkA mRNA and TrkA is enhanced in cells that normally express it (Yoon et al. 2003).

Regarding TrkB, the occurrence of mRNA for both truncated (Lomen-Hoerth & Shooter, 1995) and full-length isoforms (Laurenzi et al. 1994; Maroder et al. 1996; García-Suárez et al. 2002) has been reported. At the protein level, TrkB has been detected in thymocytes (Maroder et al. 1996; Besser & Wank, 1999; García-Suárez et al. 2002), as well as in stromal cells identified as ED1+ and F4/80+ macrophages in the rat and mouse, respectively (García-Suárez et al. 1998, 2002). In addition, TrkB expression has also been detected in morphologically identified macrophages of the bovine thymus (Levanti et al. 2001).

To our knowledge, TrkC has not been detected in the mammalian thymus at the protein level. $p75^{NTR}$ mRNA is also present in the thymus, primarily located on the stroma (Lomen-Hoerth & Shooter, 1995) in both medullar epithelial cells and dendritic cells (Parrens et al. 1998, 1999; García-Suárez et al. 2000b, 2001). Interestingly, exogenously administered NGF, or experimentally induced increased NGF plasma levels with 4-methylcatechol, have proven to induce a shift in $p75^{NTR}$ expression from medullar epithelial cells to macrophages. In fact, in control animals $p75^{NTR}$ expression was restricted to epithelial cells, whereas in the treated animals it disappeared from epithelial cells and was expressed in macrophages (García-Suárez et al. 2000b).

Trk-like proteins have also been detected in the thymus of vertebrates other than mammals (Baig & Khan, 1996; Heinrich & Lum, 2000). In the pigeon, TrkA-like expression was observed in medullar and a subpopulation of cortical epithelial cells, TrkB-like in medullar dendritic cells and cortical macrophages, and TrkC-like in scattered clusters of medullar epithelial cells, including Hassal's corpuscles (Ciriaco et al. 1996). Recently, expression of Trk-like proteins was observed in the thymus of the teleost *Dicentrarchus labrax* (Hannestad et al. 2000). Thus the presence of neurotrophins and their receptors in the thymus appears to be a feature common to most vertebrates.

NGF is present in the thymus, mostly in the medulla, and is probably synthesized locally (Katoh-Semba et al. 1993; Aloe et al. 1997; Turrini et al. 2001). Since T cells are known to produce NGF (Ehrhard et al. 1993b; Santambrogio et al. 1994; Lambiase et al. 1997), it could be hypothesized that this neurotrophin acts in a paracrine manner on the epithelial cells expressing TrkA. Such an action could account for the trophic and maturational dependency of thymic epithelial cells on thymocytes (Ritter & Boyd, 1993; Shores et al. 1994; Hollander et al. 1995; Haynes & Hale, 1998) (Fig. 4).

BDNF mRNA is present in the thymus (Laurenzi et al. 1994; Yamamoto et al. 1996; Timmusk et al. 1999), where it is expressed by stromal cells (Maroder et al. 1996), and BDNF signalling through TrkB receptors present on immature thymocytes seems to be necessary for thymocyte survival at certain developmental stages (Maroder et al. 1996) (Fig. 4). The thymus also contains mRNA and protein for NT-3 (Laurenzi et al. 1994; Katoh-Semba et al. 1996) and NT-4/5 (Timmusk et al. 1993; Laurenzi et al. 1994), but the cellular source of these polypeptides, as well as their role in thymic function, remains to be established.

Bursa of Fabricius

The bursa of Fabricius is a unique lymphoid organ present in birds, which provides the microenvironment for B-lymphocyte maturation and differentiation (Glick, 1991; Glick & Olah, 1993). Studies from our group have demonstrated the occurrence of Trk-like proteins in the pigeon bursa (Ciriaco et al. 1996, 1997). TrkA-like and TrkC-like proteins were found in the so-called follicle-associated and interfollicular epithelia, whereas TrkB-like protein was present in the bursal secretory dendritic cells. The bursa of Fabricius contains high levels of NGF during development (Ernfors et al. 1988), and this neurotrophin has been reported to increase the size of bursal lymphoid follicles (Bracci-Laudiero et al. 1991), and to reduce bursal cell mortality *in vitro* (Bracci-Laudiero et al. 1993a).

Spleen

The spleen contains detectable amounts of mRNA for all neurotrophins (Maisonpierre et al. 1990; Timmusk et al. 1993; Laurenzi et al. 1994; Yamamoto et al. 1996), but at the protein level only NT-3 has been detected in this organ (Zhou & Rush, 1993; Katoh-Semba et al. 1996). As for the receptors, $p75^{NTR}$ as well

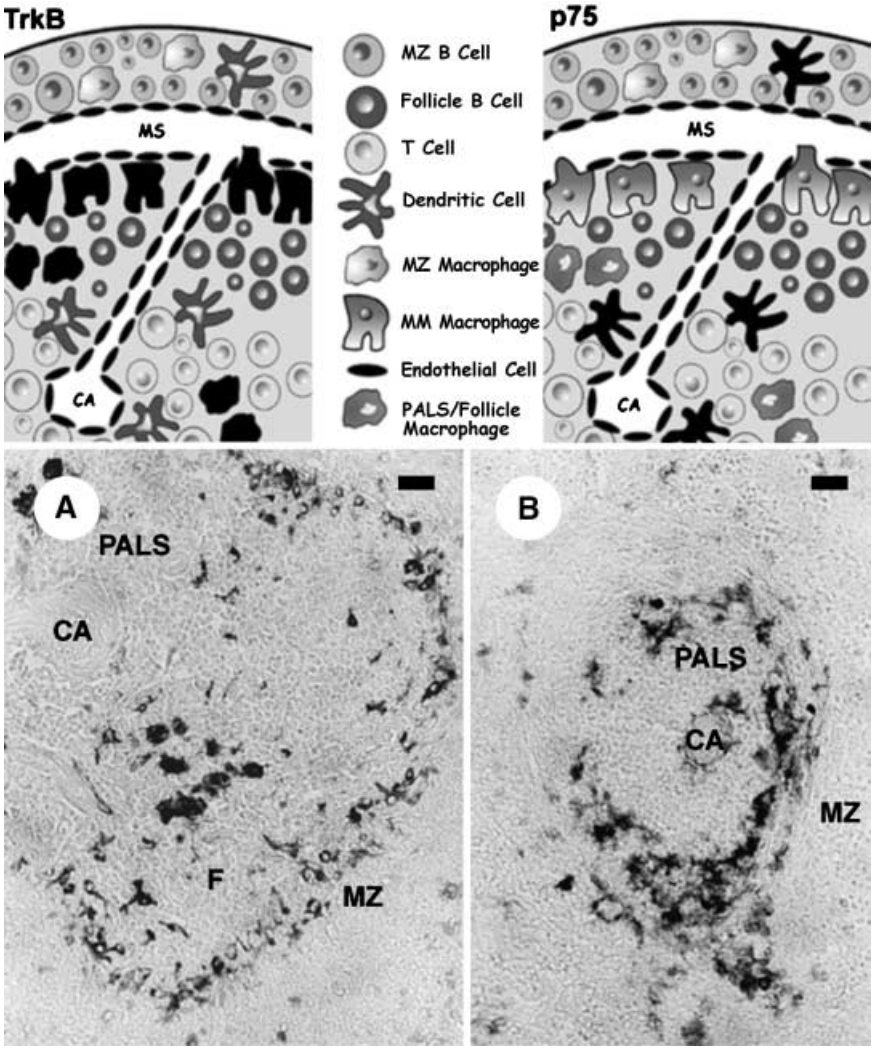

Fig. 3 The upper pictures illustrate the localization of TrkB-(left) and $p75^{NTR}$ (right)-positive cells in the rat spleen; receptor-expressing cells are represented in black. Below are shown the corresponding TrkB **(A)** and $p75^{NTR}$ **(B)** immunostained sections. TrkB-immunoreactive cells include MMM and scattered white pulp macrophages, whereas $p75^{NTR}$-positive cells are a subpopulation of dendritic cells. PALS, periarteriolar lymphatic sheath; F, follicle; MZ, marginal zone; CA, central arteriole; MM, marginal metallophilic. Scale bar = 5 μm.

as Trks have been detected at the mRNA level in human and rat spleen (Laurenzi et al. 1994; Lomen-Hoerth & Shooter, 1995; Yamamoto et al. 1996).

In humans, follicular dendritic cells express both $p75^{NTR}$ and TrkA (Labouyrie et al. 1997). By contrast, in the rat spleen $p75^{NTR}$ expression has been localized to dendritic cells in the PALS (periarteriolar lymphatic sheath, Pérez-Pérez et al. 2003), and no TrkA expression has been reported to date. TrkB has been detected in immunohistochemically identified macrophage subpopulations of human (Shibayama & Koizumi, 1996), rat (Pérez-Pérez et al. 1999) and mouse (M. Pérez-Pérez et al. unpubl. obs.) macrophages (Fig. 3).

Lymph nodes, palatine tonsils and Peyer's patches

In human palatine tonsils and lymph nodes, $p75^{NTR}$ is present in follicular dendritic cells and dendritic cells, as well as in periarteriolar macrophages (Pezzati et al. 1992; Hannestad et al. 1995; García-Suárez et al. 1997; Labouyrie et al. 1997). As for TrkA, it has been found in cryptic tonsilar epithelium, dendritic cells and interdigitated reticular cells (Hannestad et al. 1995; García-Suárez et al. 1997; Labouyrie et al. 1997). The same results applied to bovine lymphoid organs (Levanti et al. 1997, 2001).

In the pigeon caecal tonsil, a secondary gut-associated lymphoid organ, TrkA-like has been found in the

intestinal epithelium, whereas TrkB-like and TrkC-like have been detected in macrophage-dendritic cells. By contrast, BDNF-like and NT-3-like occur in the intestinal epithelium covering the lymphoid tissue, mainly in endocrine cells. Conversely, NGF-like has never been detected in this organ (Hannestad et al. 1998). In fishes (*D. labrax*), Trk-like proteins are present in the head-kidney and spleen (Hannestad et al. 2000).

Neurotrophins and immunocompetent cells

Lymphocytes

The possibility of neurotrophins acting on lymphocytes was first reported by Dean et al. (1987), who observed that NGF increased the blastogenic response of mouse spleen cells. This observation, which suggested that lymphocytes (and presumably other immunocompetent cells) expressed neurotrophin receptors, was followed by the demonstration that these cells also synthesized and released neurotrophins, which led to the proposal that there might be autocrine and paracrine actions of neurotrophins on these cells (Fig. 4). Interestingly, the expression of both neurotrophins and their receptors by lymphocytes is frequently dependent on cell activation (Kerschensteiner et al. 1999; Moalem et al. 2000).

Expression of both NGF and TrkA is induced by mitogen activation in CD4+ T cells (Ehrhard et al. 1993b), and this TrkA receptor seems to be functional because NGF administration to antigen-stimulated CD4+ T cells induces expression of c-*fos* (Ehrhard et al. 1994). Both CD4+ and CD8+ T cells produce NGF, which is increased after antigenic stimulation in the Th2 subset (Santambrogio et al. 1994; see Van Eden et al. 2002, for a review of the Th1 and Th2 cells). In additon, unstimulated human CD4+ Th1 and Th2 cells, but not Th0, express both NGF and TrkA (Lambiase et al. 1997); and Th1 cells express full-length TrkB and low levels of TrkC (Besser & Wank, 1999), and CD4+ and CD8+ T cells transcribe BDNF mRNA and produce bioactive BDNF (Braun et al. 1999; Kerschensteiner et al. 1999), NT-3 and NT-4/5 (Moalem et al. 2000). By contrast, the expression of $p75^{NTR}$ by T cells is controversial (Kittur et al. 1992; Ehrhard et al. 1993b).

In B cells, TrkA (Melamed et al. 1996; Torcia et al. 1996; D'Onofrio et al. 2000) and $p75^{NTR}$ (Brodie et al. 1996) expression has been reported. However, according to Schenone et al. (1996), B cells do not express mRNA or protein for either $p75^{NTR}$ or TrkA; these authors reported TrkB mRNA and protein expression by B cells, and demonstrated activation of these TrkB receptors by BDNF. Discrepancies between these results may be due to the activation state of these cells. Recently, the occurrence of TrkB on B cells has been confirmed (Besser & Wank, 1999; D'Onofrio et al. 2000), and the expression of TrkC suggested (D'Onofrio et al. 2000). As for neurotrophin production, B cells produce NGF (Santambrogio et al. 1994; Torcia et al. 1996) and NT-3 (Besser & Wank, 1999). Activated T cells also produce BDNF (Kerschensteiner et al. 1999). Interestingly, NGF appears to be involved in B-cell survival because it is able to rescue these cells from induced apoptosis (Kronfeld et al. 2002).

In summary, NGF/TrkA, and possibly other NT/receptor systems, seem to have a role in both T- and B-cell physiology. Furthermore, each lymphocyte subset appears to express a characteristic array of NTs and their receptors.

Monocyte-macrophage cells

Monocytes express TrkA, and this expression increases after activation, whereas it is down-regulated during differentiation towards tissue macrophages (Ehrhard et al. 1993a). As for NTs, NGF, BDNF and NT-4/5 are expressed by macrophages (Schober et al. 1998; Besser & Wank, 1999; Boven et al. 1999; Braun et al. 1999; Caroleo et al. 2001). A recent paper demonstrates that both NGF and BDNF influence the cytokine expression pattern in peripheral blood mononuclear cells, as well as in antigen-specific T cells, modulating the production of interleukin-4, and transforming growth factor-β, tumour necrosis factor-α and γ-interferon (Bayas et al. 2003).

Other cells

In bone marrow, transcripts for both $p75^{NTR}$ and all Trks are present in stromal adventitial reticular cells (Cattoretti et al. 1993; Labouyrie et al. 1999), whereas haematopoietic cells express one or several Trk receptor proteins, but not $p75^{NTR}$ (Chevalier et al. 1994; Labouyrie et al. 1999; Simone et al. 1999). Moreover, NGF is probably produced by bone marrow stromal cells (Auffray et al. 1996; Grills & Schuijers, 1998). Bone marrow cells also express TrkB (but not TrkC) as well as low levels of BDNF and NT-4/5 (but not NGF or NT-3) (Laurenzi et al. 1998).

Table 2 Immunomodulatory roles of neurotrophins

Cell type	Action	Neurotrophin	Species
B-lymphocytes	Proliferation[1,2,3]; stimulation of antibody synthesis[2,4,5,6,7]	NGF	Human, rat
	Differentiation into plasma cells[2]; expression of IL-2 receptors[3,8]; induction of CGRP synthesis[14] Survival[9,10]	NGF	Human
		NGF	Human, mouse
	Activation of Trks and signalling molecules[11,12,13]	NGF, BDNF	Human
T-lymphocytes	Proliferation[1,2]	NGF	Human, rat
	T-cell-dependent antibody synthesis[6]	NGF	Rat
	Expression of IL-2 receptors[8]	NGF	Human
	TrkB phosphorilation, survival (thymocytes)[15]	BDNF	Mouse
	Transcriptional activation of *c-fos*[15,16]	NGF, BDNF	Human, mouse
Monocytes/ macrophages	Monocytic differentiation[17]; stimulation of phagocytosis, parasite killing and IL-1β production[23]; increase in TNF-α production[25]; increase in Fcχ receptor expression[27]	NGF	Mouse
	Chemotaxis[21]	NGF, NT-3	Mouse
	Increase in nitric oxide secretion[24,25]	NT-3	Mouse
	Survival[18,19,20]; increase in oxidative burst[22]	NGF	Human
	Increase in cathepsin S expression[26]	NGF	Human
Neutrophils	Differentiation[17]	NGF	Human, mouse
	Survival[28,29]; chemotaxis[30,31]; enhancement of phagocytosis and superoxide production[28]	NGF	Mouse
Eosinophils	Differentiation[32]; survival[33]; chemotaxis[33]; release of inflamatory mediators[34]; increase in cytotoxic activity[33]; suppression of leukotriene C4 production[35]	NGF	Human
Basophils	Differentiation[32,36,37,38]; survival[39]; activation[40]; increased histamine release[41,42]; enhanced production of lipid mediators[41,42]; stimulation of IL-13 secretion[43]; modulation of IgE-mediated responses[43]	NGF	Human
Mast cells	Proliferation[44,45]; degranulation, mediator release[54,55,56,57,58,59]; survival[49,50,51,52]; chemotaxis[53]	NGF	Rat
	Differentiation[17,28,32,46,47,48]	NGF	Human, mouse
Others	Proliferation and differentiation of haematopoietic cells[60,61]	NGF	Human
	Shape change of platelets[62]	NGF	Rabbit
	Increase of vascular permeability[63]	NGF	Rat

[1]Thorpe & Pérez-Polo (1987); [2]Otten et al. (1989); [3]Brodie & Gelfand (1992); [4]Kimata et al. (1991a); [5]Kimata et al. (1991b); [6]Manning et al. (1985); [7]Brodie et al. (1996); [8]Thorpe et al. (1987); [9]Torcia et al. (1996); [10]Kronfeld et al. (2002); [11]Franklin et al. (1995); [12]Melamed et al. (1996); [13]Schenone et al. (1996); [14]Bracci-Laudiero et al. (2002); [15]Maroder et al. (1996); [16]Ehrhard et al. (1994); [17]Kannan et al. (1993); [18]Garaci et al. (1999); [19]La Sala et al. (2000); [20]Caroleo et al. (2001); [21]Kobayashi & Mizisin (2001); [22]Ehrhard et al. (1993a); [23]Susaki et al. (1996); [24]Barouch et al. (2001a); [25]Barouch et al. (2001b); [26]Liuzzo et al. (1999); [27]Susaki et al. (1998); [28]Kannan et al. (1991); [29]Kannan et al. (1992); [30]Gee et al. (1983); [31]Boyle et al. (1985); [32]Matsuda et al. (1988a); [33]Hamada et al. (1996); [34]Solomon et al. (1998); [35]Takafuji et al. (1992); [36]Matsuda et al. (1988b); [37]Tsuda et al. (1990); [38]Tsuda et al. (1991); [39]Miura et al. (2001); [40]Burgi et al. (1996); [41]Bischoff & Dahinden (1992); [42]Bürgi et al. (1994); [43]Sin et al. (2001); [44]Aloe & Levi-Montalcini (1977); [45]Aloe (1988); [46]Aloe & De Simone (1989); [47]Matsuda et al. (1991); [48]Welker et al. (2000); [49]Horigome et al. (1994); [50]Kawamoto et al. (1995); [51]Bullock & Johnson (1996); [52]Kanbe et al. (2000); [53]Sawada et al. (2000); [54]Bruni et al. (1982); [55]Mazurek et al. (1986); [56]Pearce & Thompson (1986); [57]Marshall et al. (1990); [58]Horigome et al. (1993); [59]Kawamoto et al. (2002); [60]Chevalier et al. (1994); [61]Auffray et al. (1996); [62]Gudat et al. (1981); [63]Otten et al. (1984).

Granulocytes express NGF, BDNF and NT-4/5, but not NT-3 (Laurenzi et al. 1998). Indirect evidence also suggests the occurrence of TrkA receptors in neutrophils (Kannan et al. 1991, 1992, 1993), and eosinophils (Hamada et al. 1996), which in turn produce and release NGF (Solomon et al. 1998; Kobayashi et al. 2002).

Regarding the basophil/mast cell lineage, basophils express functional TrkA receptors, but neither TrkB nor TrkC were detected in basophils (Burgi et al. 1996). Mast cells express TrkA (Horigome et al. 1993; Tam et al. 1997; Welker et al. 1998) and produce NGF (Leon et al. 1994), BDNF and NT-3 (Tam et al. 1997).

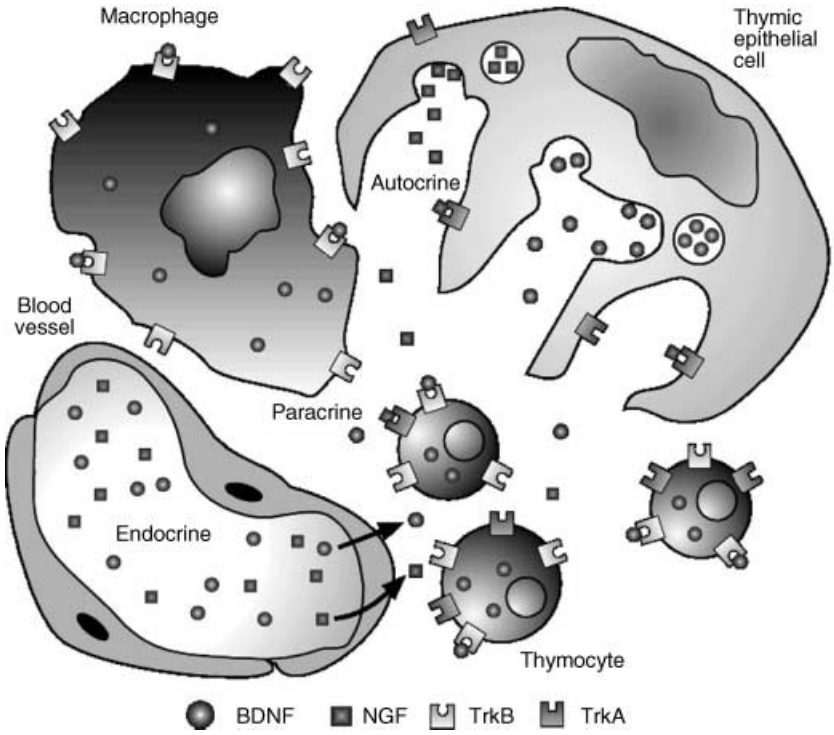

Fig. 4 Schematic representation of the possible sources and targets of NGF and BDNF in the mammalian thymus.

Data about the effects of NTs on immunocompetent cells are heterogeneous and most of them refer to NGF. Table 2 summarizes the most relevant ones.

The immune phenotype of functionally deficient TrkA and TrkB mice

Transgenic mice for NTs and their receptors have added greatly to our knowledge of the role of neurotrophins in nervous system development (see Fariñas, 1999). Occasionally, these animal models have also been used to address the question of the function of neurotrophins in other organs. The thymus of mice with a tyrosine kinase-deficient *trk*A gene product (Smeyne et al. 1994) was recently the subject of in-depth studies in our laboratory. The thymus of these animals showed numerous epithelial cell islands, thymic cysts with endodermal lining, and a much lower density of thymocytes than age-matched controls (García-Suárez et al. 2000a, 2001). This suggests that functional TrkA is necessary for the normal differentiation of the thymic epithelial primordium, and that NGF signalling through this receptor is probably important for thymic organogenesis. However, it is still uncertain whether this abnormal thymic epithelium retains the capacity to promote positive selection and to provide a suitable microenvironment for thymocytes maturation, although the low thymocyte density seems likely to result in partial or total loss of such capacities. I. Silos-Santiago (pers. commun.) demonstrated severe T- and B-cell depletion in these animals.

In functionally deficient TrkB mice, studied at postnatal day 15, the thymus showed an increase in the number of pyknotic nuclei, suggestive of apoptotic lymphocytes, especially in the cortical area. Ultrastructurally, both lymphocytes and stromal cells were strongly altered. Changes in lymphocytes consisted of abnormal morphology, fragmentation or absence of the nucleus and accumulation of cytoplasmic electron-dense bodies, which probably represented nuclear fragments with condensed chromatin. The macrophages contained numerous secondary lysosomes, whereas the epithelial cells showed cytoplasmic inclusions and vacuoles, without apparent changes in the nuclei. The TUNEL method confirmed the massive apoptosis of cortical lymphocytes in these animals. These data suggest that the TrkB ligands are involved in promoting cell survival, especially of the cortical thymocytes (García-Suárez et al. 2002). Finally, the structure of the thymus in animals lacking the gene coding for $p75^{NTR}$ was consistent with normality (García-Suárez et al. 2001).

Taken together, these results lend support to the idea that in the mammalian thymus both the NGF/TrkA and the BDNF/TrkB systems play important roles in the development and maintenance of epithelial cells and thymocytes, respectively, and that both ligand–receptor complexes are involved in the intercellular communication between these two main cell types of the thymus.

For lymphoid organs, data are still fragmentary. Results from our laboratory indicate that the spleen of newborn mice deficient in p75 shows structural changes consisting of an absence of innervating sympathetic fibers as well as a lack of incipient white pulp areas around the arterioles (Pérez-Pérez et al. 2003). By contrast, functional TrkA- or TrkB-deficient mice appear structurally normal (M. Pérez-Pérez et al. unpubl. obs.), although the possibility of a functional deficit of B cells should be addressed in further studies. Ruberti et al. (2000) observed increased cell death in the spleen of NGF-deficient adult mice.

The lymphoid organs, and especially the thymus, are richly innervated by sensory and vegetative nerve fibres that decrease with ageing (for references see Bellinger et al. 1997; Cavallotti et al. 1999, 2002). It is possible that some of the structural changes observed in the NT-receptor-deficient animals could be related to a decrease in innervation, but this has yet to be investigated.

Pathologies associated with changes in the neurotrophin system

It is well known that the nervous and immune systems interact in both health and disease, although the importance of these interactions is still a matter of debate (Kinoshita & Hato, 2001; Sternberg, 2001). Different hypotheses aimed at explaining, at least partially, the pathogenesis of several diseases have emerged on the basis of current knowledge of the role of NTs in the immune system. Some authors have suggested that NGF, and probably other NTs as well, acts as a hormone that is liberated into the bloodstream at times of stress, and in this way is able to act on immune cells throughout the body. This theory is based on the observation that NGF levels in plasma increase during stress and immunological diseases (Bonini et al. 1999). However, the fact that immune cells express both NT signalling receptors and NTs themselves suggests that they probably act on a local level and over short distances. Nevertheless, the NT/receptor complexes are likely to participate in the highly complex network of intercellular communications made up of cytokines, growth factors, neuropeptides and hormones (Mentlein & Kendall, 2000). Interleukines and other cytokines act as intermediaries in most of the inflammatory and immune actions of NTs in some diseases. There is an abundance of data on the influences of NTs on the production of other cytokines, and the influence of these on the synthesis of NTs (Aloe & Fiore, 1998; Turrini et al. 1998; Aloe et al. 1999) or their receptors (Besser & Wank, 1999) in different tissues. Nevertheless, little of this information applies to immune system cells (Screpanti et al. 1993; Marshall et al. 1999).

The inflammatory role of NGF is well known and its levels increase during inflammation, allergies and diseases of the immune system (Otten et al. 2000; Stanisz & Stanisz, 2000). Particularly important is the role of NGF in inflammatory hyperalgesia (Mendell et al. 1999; Shu & Mendell, 1999). This effect is probably due to a direct action of NGF on mast cells and sensory neurones (Woolf et al. 1996). Local production of NGF by immune cells, stimulated by IL-1β, in turn stimulated by TNFα, is probably the source of NGF (Woolf et al. 1997). Progressive tactile hyperalgesia elicited by repeated touch stimulation during inflammation is also NGF-dependent (Ma & Woolf, 1997). It has also been demonstrated recently that BDNF and NT-4/5 acting through TrkB, but not NT-3/TrkC, regulate nociceptive response to noxious heat as does NGF through TrkA (Shu et al. 1999).

In asthma and other allergic diseases, NGF levels are increased (Bonini et al. 1996; Lambiase et al. 1997; Sanico et al. 1999; Renz, 2001; de Vries et al. 2002). The bronchial hyper-reactivity of asthma is accompanied by an increase in NGF, probably produced by mononuclear cells, which enhances local Th2 responses, thereby increasing the production of IL-4, IL-5, IgG1 and IgE, but not IFN-γ nor IgG2 (Braun et al. 1998). Some of these responses may be mediated by $p75^{NTR}$ acting on Th2 cells (Tokuoka et al. 2001). Moreover, systemic NGF administration increases histamine-induced bronchial hyper-reactivity; this effect is probably mediated by tachykinins because it is abolished by a neurokinin-1 receptor antagonist, and may be exerted indirectly, via macrophages or mast cells (de Vries et al. 1999). Increased local levels of BDNF have recently been detected in allergic asthma (Braun et al. 1999).

During the development of atherosclerotic lesions in rats, there is induction of NTs and their receptors in the

vascular smooth cells, whereas in the established lesions only the expression of $p75^{NTR}$ remains, because the activation of this receptor is an inductor of the smooth cell apoptosis observed in those lesions (Wang et al. 2000). In man, NGF decreases in the atherosclerotic lesions whereas the expression of $p75^{NTR}$ is increased (Chaldakov et al. 2001).

In arthritis, NGF levels are elevated in both serum (Dicou et al. 1993) and synovial fluid (Aloe et al. 1992; Aloe & Tuveri, 1997; Halliday et al. 1998), and this increase is higher in spondyloarthritis than in rheumatoid arthritis (Dicou et al. 1996). In the knee joints of arthritic mice, IL-1β (but not TNFα) increases NGF, and NGF seems to increase TNFα (Aloe & Fiori, 1998). NGF serum levels are also higher than normal in systemic lupus erythematosus (Bracci-Laudiero et al. 1993b; Dicou et al. 1993) as well as in a murine lupus model (Bracci-Laudiero et al. 1996). Interestingly, NGF has been used successfully in the treatment of chronic vasculitic ulcers associated with rheumatoid arthritis due to the keratinocyte proliferation and the vascular neoangiogenesis promoted by this molecule (Tuveri et al. 2000).

Post-infectious and autoimmune diseases (Riikonen et al. 1998), fibromyalgia (Giovengo et al. 1999) and chronic daily headache (Sarchielli et al. 2001) course with increased levels of NGF in the cerebrospinal fluid. Interestingly, NGF receptors are up-regulated in experimental autoimmune encephalomyelitis (Oderfeld-Nowak et al. 2001), and a gene therapy approach has been used experimentally, with good results, to down-regulate the expression of $p75^{NTR}$ (Soilu-Hanninen et al. 2000).

As for skin, in psoriatic keratinocytes NGF levels are increased, and NGF acts as a mitogen for these cells and as a T-cell activator (Raychaudhuri et al. 1998). In AIDS, patients with Kaposi's sarcoma show higher NGF levels than patients without Kaposi's sarcoma, and also higher than in those with non-AIDS Kaposi, and these tumour cells express TrkA and proliferate when exposed to NGF (Pica et al. 1998). In prurigo nodularis NGF is overexpressed in the skin (Johansson et al. 2002).

It is possible that studies of transgenic mice will contribute greatly to our understanding of the possible role of NTs in the immune system, and the importance of these growth factors in health and disease (García-Suárez et al. 2000a, 2001, 2002). This is the case for an extremely rare disorder called congenital insensitivity to pain with anhidrosis (CIPA), which has recently been shown to be caused by a mutation in the trkA gene (Indo et al. 1996; Mardy et al. 1999; Kobayashi et al. 2002). Patients with this disorder show neuronal deficits similar to those of trkA knockout mice. Furthermore, despite their normal serum immunoglobulin levels, they show frequent infections, especially osteomyelitis, indicating a possible defect in B-cell function. These findings are of interest, taking into account the aforementioned data on the possible role of the NGF/TrkA system in B cells. Unpublished data by I. Silos-Santiago and colleagues demonstrate that mice lacking functioning trkA have a strong immunodeficiency affecting both T and B cells.

Concluding remarks and future directions

Through their widespread expression in the immune organs and immunocompetent cells, NTs are candidate molecules for regulating immune as well as neuroimmune interactions. Accurate studies in transgenic and knockout mice, especially in adult surviving animals, are revealing hitherto unknown roles of NTs *in vivo.* This will open up new perspectives for a potential therapeutic use of NTs when pathologies are due to the absence, increased or defective production of NTs, or by mutations in their receptors.

Based on the available data mentioned in this review, it seems likely that NTs may be involved in immune pathologies. Thus an altered concentration of circulating or tissular NGF levels is associated with autoimmune inflammatory diseases, allergic diseases and parasitic infections. Furthermore, NTs, or dysregulation of NT receptor expression, may be involved in regulating the growth, differentiation and apoptosis of some kinds of non-neuronal tumours (see for a review Rubin & Segal, 2003), such as pancreatic ductal adenocarcinoma (Miknyoczki et al. 1999), melanoma (Innominato et al. 2001), prostate cancer (Satoh et al. 2001) and lung cancer (Ricci et al. 2001).

In the past few years, NTs and in particular NGF have been used with varying degrees of success in a variety of disorders, including peripheral metabolic and toxic neuropathies (Pradat et al. 2002; Apfel, 2002), spinal cord injuries (Blesch et al. 2002; Bregman et al. 2002; Murray et al. 2002), neurodegenative diseases (Batchelor et al. 1999; see also Dechant & Barde, 2002), and cutaneous (Matsuda et al. 1998) and corneal (Lambiase et al. 2000) wound repair. In tumours the Trk receptors

are also viable molecular targets for medical intervention (see Ruggeri et al. 1999; Miknyoczki et al. 2002). Regarding diseases in which the immune system is particularly involved, NGF has proved to have useful effects in vasculitis-induced rheumatoid arthritis (Tuveri et al. 2000; Aloe, 2001) and is now being considered as a new therapeutic strategy in the blockade of NT overexpression during the allergic or inflammatory process. Nevertheless, it must be emphasized that there are serious pharmacological problems with the use of NTs in human therapy, especially because of the manner and site of administration. Virus transfer and the transplantation of engineered cells, which have been performed experimentally, may represent promising perspectives for NT delivery or NT-receptor blocking in the near future.

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