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Expression and Role of the TrkA Receptor in Pulmonary Inflammatory Diseases

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1. Introduction

The nerve growth factor NGF belongs to the neurotrophin family and was described for the first time more than fifty years ago by Rita Levi-Montalcini and collaborators (Levi-Montalcini et al., 1995; Levi-Montalcini & Hamburger, 1951), who showed its major role in neuronal growth and survival. NGF effects are mediated by activation of two receptor types: the low-affinity p75 receptor for neurotrophins ($p75^{NTR}$) and the high-affinity tropomyosin-related kinase A (TrkA) receptor (Freund-Michel & Frossard, 2008a). The $p75^{NTR}$ receptor belongs to the death receptor family and its activation by NGF at nanomolar concentrations leads either to pro- or anti-apoptotic signalling pathways. The $p75^{NTR}$ receptor is not selective for NGF as it can also bind pro-neurotrophins and the other neurotrophins at the same nanomolar concentrations (Chao, 2003). Inversely, the TrkA receptor is selective for NGF and belongs to the tyrosine-kinase receptor family. Its activation by NGF at picomolar concentrations activates signalling pathways inducing cell proliferation, differentiation and survival in particular through activation of phosphatidylinositol-3 kinase (PI3K), small protein G Ras, phospholipase Cβ (PLCβ) and mitogen-activated protein kinases (MAPK) (Freund-Michel & Frossard, 2008a).

The role of NGF in neuronal growth and survival has been widely studied and led to consider NGF as a promising therapeutic target in several pathologies of the nervous system, in particular neurodegenerative diseases (Prakash et al., 2010). In addition, many studies have suggested that NGF also plays the role of an inflammatory mediator, in particular in the lung (Freund-Michel & Frossard, 2008a). Indeed, numerous sources of NGF have been described in the lung, including infiltrated inflammatory cells, sensory nerves, and many lung structural cells such as fibroblasts, epithelial, endothelial, and

airway or pulmonary vascular smooth muscle cells (Ricci et al., 2004b). These cells have been shown to release more NGF in inflammatory conditions, and may thus participate in increased NGF levels observed in pulmonary inflammatory diseases. In parallel, many studies have shown an active role of NGF in pulmonary inflammation, airway sensory nerve plasticity, airway and vascular hyperreactivity and remodelling (Freund-Michel & Frossard, 2008a). Most of these NGF effects occur through activation of the TrkA receptor, thus highlighting the pivotal role played by this receptor in pulmonary inflammatory diseases.

The aim of the present chapter is to describe the role of the TrkA receptor activated by NGF in pulmonary inflammatory diseases. We will first present the TrkA receptor by describing its discovery, its structure and activity as well as its major signalling pathways. We will then focus on the TrkA receptor in the lung, by describing its pulmonary expression and review its involvement in NGF-mediated effects in the lung. We will describe in particular how the TrkA receptor participates to NGF-induced inflammation, airway and vascular hyperreactivity and remodelling in the lung, focusing on two major pulmonary diseases: asthma and pulmonary hypertension.

2. Presentation of the TrkA receptor

The TrkA receptor belongs to the Trk receptor family, together with TrkB and TrkC receptors. Each Trk receptor binds with a picomolar affinity to a preferred ligand: NGF for TrkA, BDNF (brain-derived neurotrophic factor) and NT-4/5 (neurotrophin-4/5) for TrkB, and NT-3 (neurotrophin-3) for TrkC (Chao, 2003). However, some crosstalks have been described, in particular for NT-3 being able to bind TrkA and TrkB receptors but at higher concentrations (Ryden & Ibanez, 1996).

2.1 Discovery of the TrkA receptor

A proto-oncogene was identified in 1986 by Martin-Zanca and co-workers in human colon carcinomas (Martin-Zanca et al., 1986). This proto-oncogene, resulting from fusion between genes encoding for a tyrosine-kinase domain and a non muscular tropomyosin, was named NTRK or trk for « tropomyosin-related kinase ». Three isoforms were identified and named NTRK1 (or TRKA), NTRK2 (or TRKB) and NTRK3 (or TRKC), with proteins encoded by these genes named Trk (TrkA, TrkB and TrkC) (Martin-Zanca et al., 1986). Expression of Trk proteins was later also detected in thyroid carcinomas and other cancers such as melanomas or breast cancers, as well as in non cancer tissues, in particular in the nervous system (Greco et al., 1997). In 1991, the TrkA protein was identified as the high affinity receptor for NGF (Kaplan et al., 1991a; Klein et al., 1991).

2.2 Structure of the TrkA receptor

The human TrkA receptor is encoded by a gene of 23kb located on chromosome 1q21-q22 (Weier et al., 1995). This gene contains 16 introns of 70bp to 3.3kb and 17 exons of 18 to 394bp (Indo et al., 1997), with the 9 first exons encoding for the extracellular part of the receptor (Metsis, 2001). The TrkA protein contains 790 amino acids with a molecular weight of 140 kDa (Meakin & Shooter, 1992), and is composed of an intracellular domain containing a tyrosine-kinase intrinsic activity, a unique transmembrane helix, and an extracellular

domain dedicated to NGF binding (Wiesmann & de Vos, 2001). This extracellular domain is highly glycosylated, which is essential for activation of TrkA signalling pathways (Friedman & Greene, 1999).

Alternative splicing leads to several isoforms of the TrkA receptor. TrkA I and TrkA II splice variants differ only in the presence or absence of a 6 amino acid sequence. However, even if TrkA II expression is restricted to the nervous system, whereas TrkA I is more ubiquitously expressed (Clary & Reichardt, 1994), no differences in NGF binding or in TrkA function have been identified between these two isoforms (Barker et al., 1993). More recently, a novel hypoxia-regulated TrkA III splice variant has also been described: this isoform is expressed on internal membranes (Tacconelli et al., 2005) and exhibits oncogenic activity (Farina et al., 2009). Finally, a metalloproteinase-dependent cleavage of TrkA extracellular domain has been described, with release of a soluble fragment whose function remains unknown (Cabrera et al., 1996). In parallel, this cleavage induces activation of TrkA intracellular kinase domain, thus providing a TrkA NGF-independent activation, which may contribute to TrkA-dependent effects *in vivo* (Diaz-Rodriguez et al., 1999).

2.3 Activation and signalling pathways of the TrkA receptor

As classically described for other tyrosine-kinase receptors, NGF binds to the extracellular domain of the TrkA receptor and induces its dimerization thereby activating its intracellular tyrosine kinase domain (Kaplan et al., 1991b). Each kinase domain induces phosphorylation of three tyrosine residues (Y670, Y674 and Y675) on the contralateral kinase domain (Mitra, 1991), thus leading to enhancement of kinase activity and further phosphorylation of three other tyrosine residues outside the kinase domain (Y490, Y751 and Y785) (Stephens et al., 1994). These newly phosphorylated tyrosine residues are then recognized by proteins through their SH2 (Src homology domain 2) domains. The adapter protein Shc (Src homology 2-containing protein) interacts with the phosphorylated Y490 residue, phosphatidyl-inositol 3-kinase (PI3K) interacts with the phosphorylated Y751 residue, and phospholipase Cγ (PLCγ) interacts with the phosphorylated Y785 residue, thereby initiating three main signalling pathways that have been widely studied in particular in neuronal cells (Skaper, 2008). However, some recent studies also show activation of these TrkA signalling pathways in non neuronal cells, and in particular in the airways (for reviews: Freund-Michel & Frossard, 2008a; Prakash et al., 2010).

2.3.1 Ras/Raf pathway

Shc intracellular binding to the TrkA receptor leads to phosphorylation of its tyrosine residues and further recognition by the adapter protein Grb-2 (growth factor receptor bound protein-2) through SH3 (Src homology domain 3) domains. Grb-2 then binds to the factor sos (factor son of sevenless) to induce recruitment of the small G protein Ras to the cell membrane and its activation (Segal & Greenberg, 1996). This translocation to the cell membrane enables Ras-induced activation of the Raf kinase and therefore phosphorylation of Raf and activation of the MAPK (mitogen-activated protein kinase) ERK1/2 (extracellular-regulated protein kinase 1/2), leading to activation of survival mechanisms and proliferation (Freund-Michel et al., 2006). Concomitant activation of Rap1, another small

G protein, can potentiate Ras activation and enhance activation of the ERK1/2 pathway (York et al., 2000).

2.3.2 PI3K pathway

PI3K intracellular binding to the TrkA receptor leads to its phosphorylation and activation. PI3K then induces synthesis of phosphatidyl-inositol 3,4-bisphosphate that recruits PDK-1 (phosphoinositide-dependent kinase-1) to the cell membrane and induces activation of PKB (protein-kinase B, also called Akt) (Ashcroft et al., 1999). PKB then leads to activation of gene transcription, either through activation of the small G protein Rac and the MAPK pathway (Kita et al., 1998; Yamaguchi et al., 2001), or through activation of the atypical PKC zeta in a MAPK-independent manner (Wooten et al., 1994). In addition, PKB can lead to activation of proteins belonging to the IAP (inhibitors of apoptosis) family that are involved in cell survival (Wiese et al., 1999). Finally, a Ras-dependent activation of PI3K has also been described, through direct interaction between Ras and PI3K in a complex also containing the adapter protein Gab-1 (Grb2-associated binder-1) after activation of Shc and Grb-2 (Holgado-Madruga et al., 1997; Korhonen et al., 1999).

2.3.3 PLC/PKC pathway

PLCγ is activated by its interaction with the TrkA receptor and its phosphorylation by TrkA intrinsic kinase domains. PLCγ then induces cleavage of phosphatidyl inositol 4,5-bisphosphate into inositol trisphosphate (IP_3) and diacylglycerol (DAG). DAG activates protein-kinase C (PKC) to activate the MAPK pathway, with in particular activation of JNK (c-jun N-terminal kinase) and p38 (Patapoutian & Reichardt, 2001). IP_3 binds to its receptor localized on the endoplasmic reticulum and induces calcium release into the cell cytoplasm, thus contributing to PKC activation (Obermeier et al., 1993).

2.4 Transactivation of the TrkA receptor by G protein-coupled receptors

Neurotrophin-independent activation of Trk receptors, and in particular of the TrkA receptor, has been evidenced in rat neuronal cells after adenosine treatment (Lee & Chao, 2001). Activation of the adenosine A_{2A} receptor, a G protein-coupled receptor (GPCR), induces activation of a kinase belonging to the Src family that is then able to phosphorylate the TrkA receptor and activate the PI3K/PKB pathway (Lee & Chao, 2001; Lee et al., 2002a). This effect has also been evidenced with another GPCR agonist, the pituitary adenylate cyclase-activating peptide (PACAP), being able to induce TrkA transactivation and specific activation of the PI3K/PKB pathway in absence of NGF (Lee et al., 2002b). Since neuroprotective effects of adenosine and PACAP had been previously demonstrated, it has been suggested that this TrkA transactivation mechanism may contribute to these neuroprotective effects through activation of PI3K/PKB (Lee et al., 2002b). However more recent studies suggested that this TrkA transactivation mechanism occurred on newly synthesized TrkA receptors that were not already expressed at the cell membrane (Rajagopal et al., 2004).

2.5 Trafficking of the TrkA receptor

NGF activation of the TrkA receptor expressed on neurons can activate signalling pathways close to the nucleus through a specific mechanism called retrograde transport (Heerssen &

Segal, 2002). Once activated by NGF, the TrkA receptor is internalized, mainly through activation of three mechanisms: clathrine-dependent internalization, caveolae-dependent internalization, or macroendocytosis (Philippidou et al., 2011; Zweifel et al., 2005). All these mechanisms are involved in TrkA internalization and depend i) on the cell type studied, ii) on the concentration of NGF, and iii) on the amplitude of the signal generated by TrkA activation (Zweifel et al., 2005). Once internalized, only a few number of TrkA receptors are transported close to the nucleus, using early endosomes characterized by expression of the small G protein Rab5 and its effector EEA1 (Early endosome antigen 1) (Delcroix et al., 2003). TrkA retrograde transport is dependent upon activation of the PI3K-PKB pathway (Delcroix et al., 2003; Kuruvilla et al., 2000; York et al., 2000). Most of internalized TrkA receptors are either degraded through targeting to lysosomes (Jullien et al., 2002; Saxena et al., 2005) or to the proteasome after ubuquitination (Georgieva et al., 2011; Takahashi et al., 2011), or recycled at the cell membrane (Chen et al., 2005).

3. TrkA expression in the lung

Neurotrophin expression was first described in the central and peripheral nervous systems, participating to nerve growth and survival through activation of Trk and $p75^{NTR}$ receptors. However, neurotrophins and their receptors were later also described in a variety of non-neuronal tissues, and in particular in the lung (Lomen-Hoerth & Shooter, 1995).

3.1 *In vitro* studies

3.1.1 Inflammatory cells

NGF expression, which was first reported in T lymphocytes (Ehrhard et al., 1993a), was later also described in a variety of inflammatory cells including B lymphocytes (Torcia et al., 1996), mast cells (Leon et al., 1994), eosinophils (Solomon et al., 1998) and macrophages (Ricci et al., 2000b). Expression of the TrkA receptor was shown on mast cells (Tam et al., 1997), Th2 lymphocytes (Ehrhard et al., 1993a; Lambiase et al., 1997), B lymphocytes (Torcia et al., 1996), eosinophils (Hahn et al., 2006; Nassenstein et al., 2003; Noga et al., 2002), monocytes and macrophages (Ehrhard et al., 1993b; Otten et al., 1994), and basophils (Burgi et al., 1996).

3.1.2 Airway structural cells

Many airway structural cells such as fibroblasts (Antonelli et al., 2005; Olgart & Frossard, 2001), epithelial cells (Fox et al., 2001; Pons et al., 2001), airway smooth muscle cells (Freund et al., 2002), pulmonary endothelial and vascular smooth muscle cells (Freund-Michel et al., 2009) are sources of NGF (**Fig. 1**). Investigation of TrkA expression on these cells showed TrkA expression in particular on pulmonary fibroblasts (Micera et al., 2001), airway smooth muscle cells (Dagnell et al., 2007; Freund-Michel et al., 2006; Freund-Michel & Frossard, 2008b), airway epithelial cells (Othumpangat et al., 2009), and pulmonary endothelial and vascular smooth muscle cells (Freund-Michel et al., 2010) (**Fig. 1**).

3.2 *In vivo* studies

Expression of TrkA mRNA was initially evidenced in rat and human lung homogenates (Barbacid et al., 1991; Lomen-Hoerth & Shooter, 1995). Expression of TrkA protein was then

shown by immunohistochemistry in isolated human alveolar macrophages (Ricci et al., 2000b), in isolated extrapulmonary arteries (Ricci et al., 2000a), and was later also evidenced on human airway and vascular smooth muscles, on alveolar cells, on airway sensory nerves, as well as on infiltrated inflammatory cells, in particular macrophages, mast cells and lymphocytes (Kassel et al., 2001; Olgart Hoglund et al., 2002; Ricci et al., 2004b). Similar TrkA expression was shown in the mouse lung (Hikawa et al., 2002; Nassenstein et al., 2006).

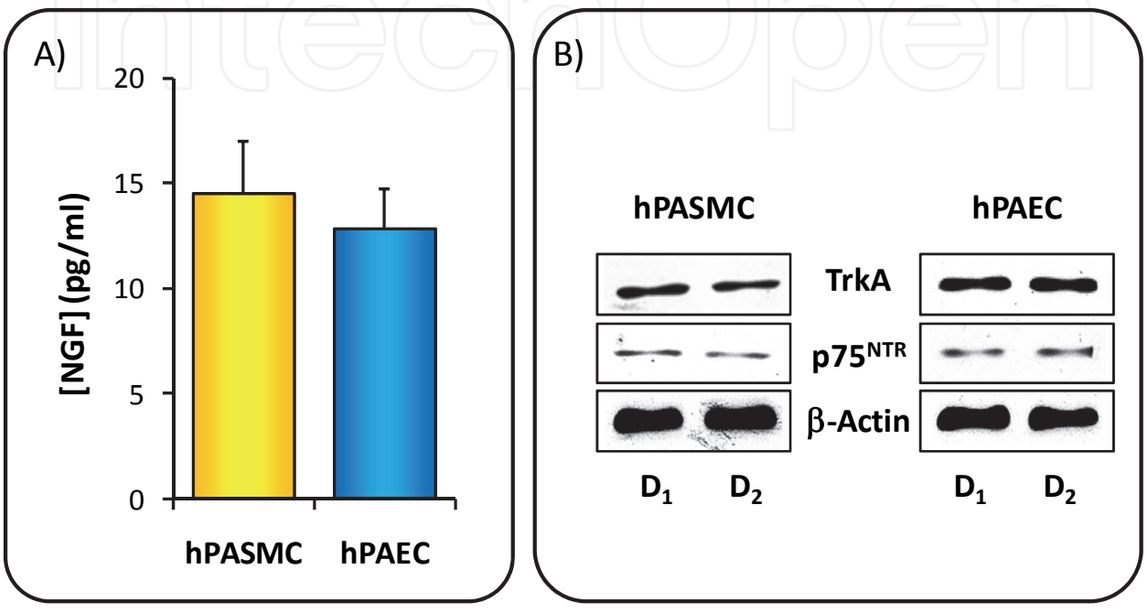

Fig. 1. Expression of NGF and its receptors in human pulmonary vascular cells

A) NGF protein levels (pg/ml) secreted after 24h by human pulmonary arterial smooth muscle cells (hPASMC) or human pulmonary arterial endothelial cells (hPAEC) in primary culture were assessed by ELISA in the culture cell supernatant. Data are means ± S.E.M. of n=3 experiments performed in triplicates with cells from two different donors. B) TrkA and $p75^{NTR}$ proteins were detected by Western blotting in cultured hPASMC or hPAEC from two different donors (D1 and D2), with rabbit polyclonal anti-human TrkA or $p75^{NTR}$ antibodies as specific protein bands of 140 and 75 kDa respectively. β-Actin probed in the same blots was used to control for protein loading.

4. NGF effects in the lung mediated by activation of the TrkA receptor

NGF is able to stimulate inflammatory cells infiltrated in the bronchial mucosa, promoting in particular their activation and survival in the airways (Freund-Michel & Frossard, 2008a). NGF also displays its role of growth factor on airway nerves, in particular on sensory airway nerves (Hoyle et al., 1998), and is able to stimulate other airway structural cells such as pulmonary fibroblasts or airway smooth muscle cells (Freund-Michel & Frossard, 2008a). Some of these effects involve activation of the TrkA receptor expressed on these cells (**Fig. 2**).

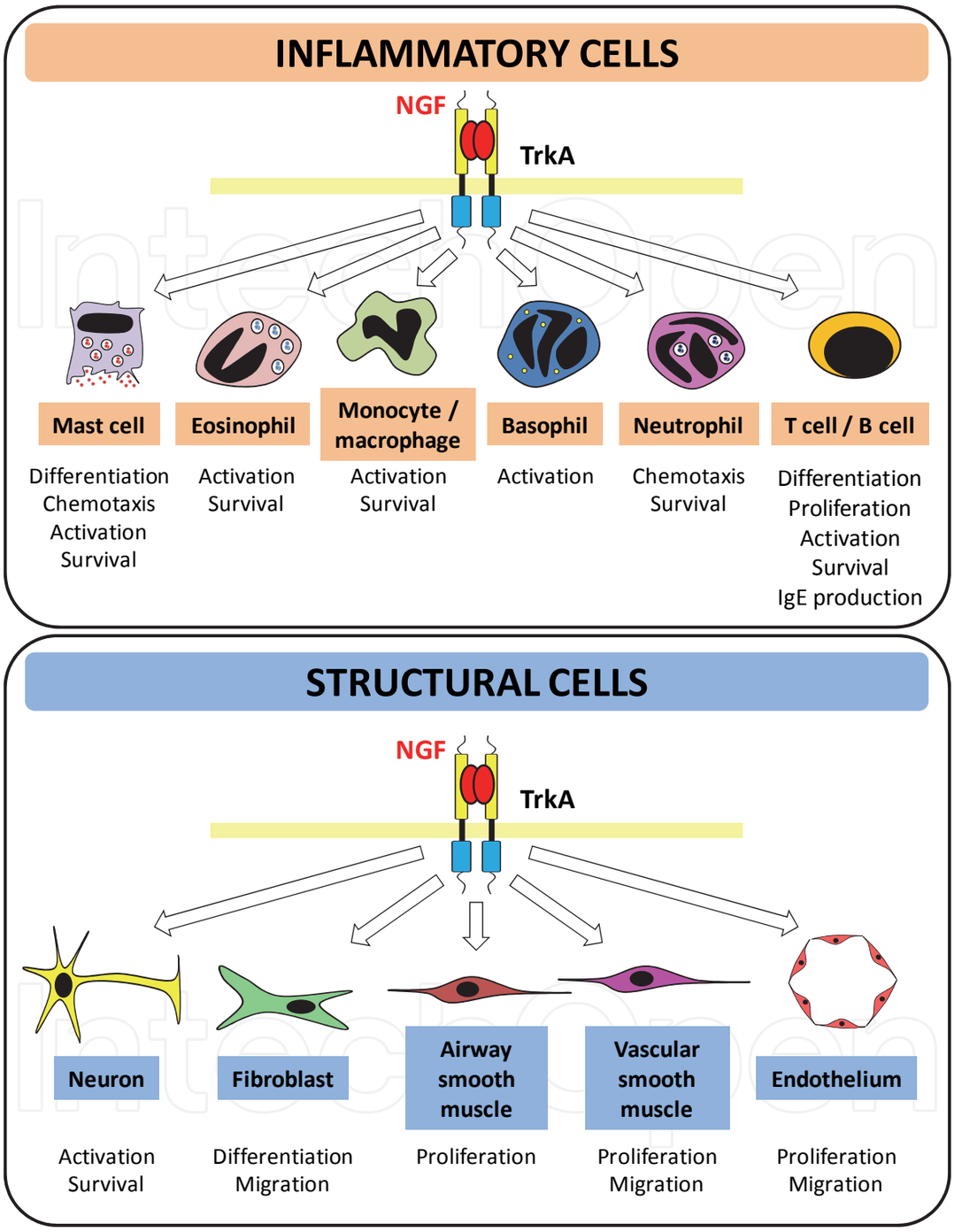

Fig. 2. NGF effects in the lung mediated via activation of the TrkA receptor

NGF-induced activation of the TrkA receptor participates to attraction and activation of inflammatory cells in the lung and may therefore contribute to lung inflammation. The TrkA receptor is also expressed on lung structural cells and participates to NGF-induced effects that may contribute to altered reactivity and remodelling processes existing in pulmonary inflammatory diseases.

4.1 TrkA and inflammatory cells

4.1.1 Mast cells

In vitro, activation of the TrkA receptor by NGF induces granule formation in immature mast cells and therefore contributes to their differentiation (Kim et al., 2008). In addition, NGF is a chemotactic factor for mast cells through both MAPK and PI3K signalling pathways following TrkA activation (Sawada et al., 2000). TrkA activation is also involved in NGF-induced degranulation of mast cells and mediators release such as for example chemokines (Ahamed et al., 2004), or serotonin (Kawamoto et al., 2002). Finally, NGF acts as a key factor to promote mast cell survival through TrkA-induced suppression of apoptosis (Kawamoto et al., 1995). *In vivo*, a correlation between NGF levels in bronchoalveolar lavage (BAL) fluids and the number of mast cells infiltrated in the bronchial mucosa has been evidenced in asthmatic patients after allergenic challenge (Kassel et al., 2001). Expression of TrkA receptors on these mast cells therefore suggests a role for this receptor in NGF-induced attraction and survival of these cells in the lung *in vivo* (Kassel et al., 2001).

4.1.2 Basophils

In vitro, NGF potentiates mediator release from human basophils as well as primes the cells to produce leukotriene C4, and these effects are TrkA-dependent (Burgi et al., 1996). NGF can also modulate IgE-mediated responses in human basophils, and these effects are enhanced on cells from allergic subjects (Sin et al., 2001). However, flow cytometry studies revealed no significant differences in TrkA receptor expression on basophils in this study (Sin et al., 2001).

4.1.3 T and B cells

Although various effects of NGF have been described on T lymphocytes, few studies have investigated the role of the TrkA receptor in these effects. Only one study by Ehrhard and co-workers clearly demonstrates involvement of the TrkA receptor in NGF-induced activation of T lymphocytes *in vitro* (Ehrhard et al., 1994). *In vivo*, NGF effects on T lymphocytes remain controversial, since two studies conducted in a mouse model of asthma failed to show NGF-related effects on T cells (Braun et al., 1998; Path et al., 2002). However, in a transgenic mouse tissue-specifically overexpressing NGF in the lung, increased numbers of T lymphocytes have been shown in the lung after allergenic challenge (Quarcoo et al., 2004). The role of NGF and its TrkA receptor on T lymphocytes in pulmonary inflammatory diseases needs therefore to be further clarified *in vivo*.

NGF has been shown to induce proliferation of B lymphocytes *in vitro*, and this effect occurs through activation of the TrkA receptor and its signalling pathways involving PLCγ, PI3K and MAPK (Melamed et al., 1996). NGF-induced activation of the TrkA receptor also participates to B cell survival through PI3K-dependent activation of PKC zeta (Kronfeld et al., 2002). *In vivo*, in mice lacking TrkA in non-neuronal tissues, all major immune system cell populations were present in normal numbers and distributions, excepted for B lymphocytes, demonstrating that endogenous NGF modulates B cell development through activation of the TrkA receptor (Coppola et al., 2004). Moreover, during allergic airway inflammation in the mouse *in vivo*, NGF contributes to B cell differentiation into plasma cells and activates the TrkA receptor to enhance plasma cell survival and production of immunoglobulins E (Abram et al., 2009).

4.1.4 Eosinophils

In vitro, eosinophil degranulation is promoted by NGF-induced activation of the TrkA receptor, inducing release of inflammatory mediators such as interleukin-4 (Noga et al., 2002). *In vitro* NGF treatment of eosinophils from patients with allergic bronchial asthma increases viability of these cells, and this effect is correlated to increased expression of the TrkA receptor on eosinophils (Nassenstein et al., 2003). In addition, coculture of lung eosinophils with airway epithelial cells resulted in enhanced epithelial neurotrophin production, as well as in prolonged survival of eosinophils (Hahn et al., 2006). Complete inhibition of eosinophil survival in the presence of the TrkA kinase inhibitor K252a confirmed the important role of the TrkA receptor in eosinophil survival (Hahn et al., 2006).

4.1.5 Monocytes / macrophages

NGF induces TrkA activation in monocytes *in vitro* to trigger a respiratory burst, the major component of monocyte cytotoxic activity (Ehrhard et al., 1993b). Activation of the TrkA receptor by NGF also promotes monocytes survival (la Sala et al., 2000). TrkA transactivation mechanisms with GPCR ligands, recently evidenced in monocytes, contribute to pro-inflammatory activities such as for example synthesis of reactive oxygen species (El Zein et al., 2007, 2010). Expression of the TrkA receptor was shown to decrease during *in vitro* differentiation of monocytes to macrophages, suggesting a maturation-dependent regulation of TrkA expression in these cells (Ehrhard et al., 1993b).

NGF was reported to activate macrophages *in vitro* in the process of inflammatory and immune actions, inducing phagocytosis, parasite killing, and production of inflammatory cytokines in a TrkA dependent-manner (Barouch et al., 2001; Susaki et al., 1996). *In vivo*, TrkA expression was reported on human alveolar macrophages (Ricci et al., 2004b; Ricci et al., 2000b), and the TrkA receptor and its binding protein SH2-Bβ participate to activation of alveolar macrophages *in vivo* in a guinea pig model of asthma (Li et al., 2009).

4.1.6 Neutrophils

In a murine model of rhinitis induced by toluene diisocyanate exposure, a massive increased number of neutrophils in the nasal mucosa correlates to increased levels of NGF (Wilfong & Dey, 2004 & 2005). Neutrophil infiltration was inhibited after *in vivo* pre-treatment with the TrkA kinase inhibitor K252a, thus showing the important role of the TrkA receptor on neutrophil attraction in the nasal mucosa (Wilfong & Dey, 2004).

4.2 TrkA and airway structural cells

A role for the TrkA receptor has been evidenced in NGF-induced effects on airway sensory nerves. In particular, NGF induces release of neuropeptides such as substance P by airway neurons, and this effect is TrkA-dependent (de Vries et al., 2006; Dinh et al., 2004). A similar effect has been reported in nasal sensory neurons (Wilfong & Dey, 2004). NGF induces proliferation of airway smooth muscle cells through activation of the TrkA receptor (Freund-Michel et al., 2006). We also showed that NGF multiple stimulation of these cells induce internalization and degradation of the TrkA receptor followed by upregulated re-synthesis of functional TrkA receptors and increased proliferative effect (Freund-Michel & Frossard, 2008b). In ongoing studies, we have recently found that NGF induces proliferation and migration of human pulmonary endothelial and vascular smooth muscle cells *in vitro*,

and that these effects are inhibited by pre-treatment with the TrkA kinase inhibitor K252a, thus suggesting a role for the TrkA receptor in these NGF-mediated effects (Freund-Michel et al., 2009) (**Fig. 3**).

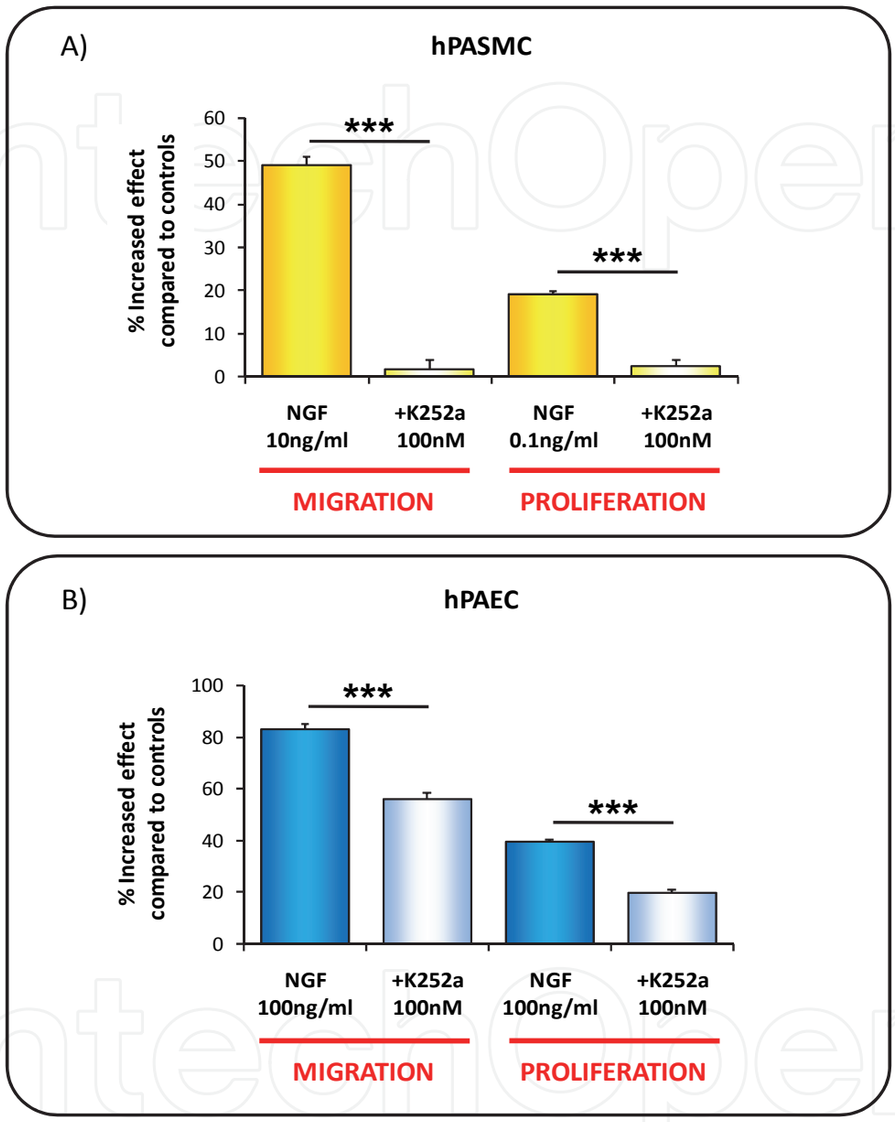

Fig. 3. Involvement of the TrkA receptor in NGF-induced effects on human pulmonary vascular cells.

Effect of NGF (0.1, 10 or 100 ng/ml) after 24h on A) human pulmonary arterial smooth muscle cells (hPASMC) or B) human pulmonary arterial endothelial cells (hPAEC) in primary culture. Cell proliferation was assessed by the BrdU technique and cell migration was evaluated by the Transwell assay. Data are presented as the maximal percentage of increased proliferation or migration compared to untreated control cells. NGF effect was evaluated in the presence or absence of the TrkA kinase inhibitor K252a (100nM, 30min pre-treatment followed by 24h concomitant treatment with NGF). ***: $P<0.001$ versus NGF alone with n=5 independent experiments performed in triplicates with cells from two different donors.

5. Role of the TrkA receptor in pulmonary inflammatory diseases

Circulating NGF levels are increased in human allergic and inflammatory diseases (Bonini et al., 1996). A local increase in NGF secretion has also been evidenced in BAL fluid from asthmatic patients (Kassel et al., 2001; Olgart Hoglund et al., 2002). In addition, our ongoing studies show that pulmonary arteries from patients suffering from pulmonary hypertension secondary to chronic obstructive pulmonary diseases (COPD) secrete more NGF than pulmonary arteries from control donors (Freund-Michel et al., 2010). Asthma and pulmonary hypertension share in common three major features occurring either in airways or in pulmonary arteries: inflammation, tissue hyperreactivity and remodelling (Barnes, 2010; Broide et al., 2011; Hassoun et al., 2009; Humbert, 2010). Several *in vitro* and *in vivo* studies suggest that NGF may play a role in these three physiopathological mechanisms, in particular through activation of the TrkA receptor (**Fig. 4**).

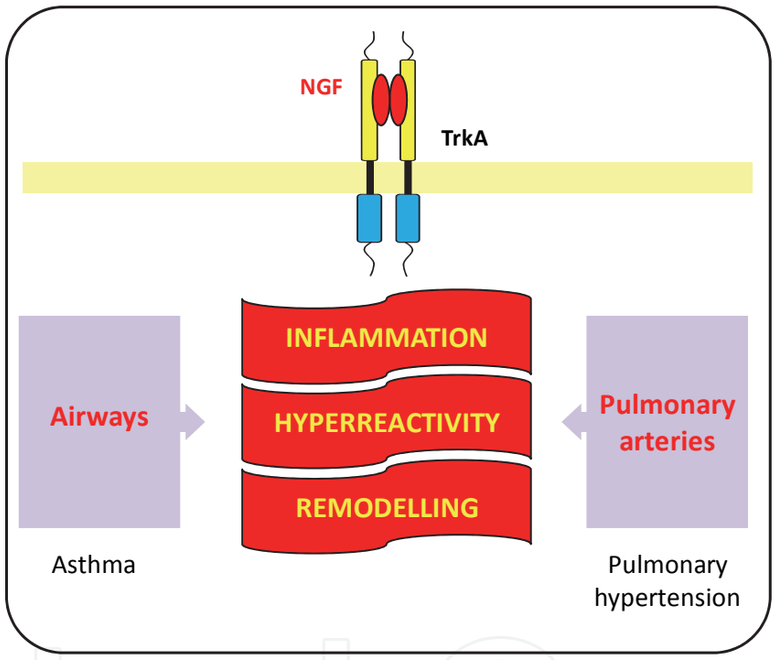

Fig. 4. Potential role of the TrkA receptor in asthma and pulmonary hypertension

In vitro and *in vivo* studies suggest that activation of the TrkA receptor by NGF contributes to inflammation as well as tissue remodelling and altered reactivity, three features occurring in particular in airways and in pulmonary arteries and playing a major role in the physiopathology of asthma and pulmonary hypertension.

5.1 NGF, TrkA and inflammation

5.1.1 Asthma

In a mouse model of asthma, NGF inhibition induced by blocking antibodies administered *in vivo* decreases airway inflammation (Braun et al., 1998; Path et al., 2002). On the contrary, allergen sensitization and challenge in a transgenic mouse tissue specifically overexpressing NGF in the lung displays greater airway inflammation (Path et al., 2002; Quarcoo et al., 2004). *In vivo* administration of a pan-Trk receptor decoy in a mouse model of asthma

reduces interleukin-(IL-)4 and IL-5 cytokine levels (Nassenstein et al., 2006). Substance P is one of the neuropeptides released by airway sensory nerves that participates to neurogenic inflammation in asthma (Quarcoo et al., 2004). *In vivo* treatment with the TrkA kinase inhibitor K252a prevents the increase in substance P observed in a guinea pig model of asthma (de Vries et al., 2006). *In vivo* pre-treatment with TrkA blocking antibodies decreases IL-1β and IL-4 levels in the BAL fluid after allergen sensitization and challenge in the guinea pig (Li et al., 2009). Similar results are observed with TrkA blocking antibodies in a mouse model of asthma (Ni et al., 2010). Altogether, these results show a major role of NGF in airway inflammation through activation of its TrkA receptor.

5.1.2 Pulmonary hypertension

We recently showed that NGF stimulates secretion of inflammatory cytokines such as IL-1β and tumor necrosis factor-α from rat and human pulmonary arteries (Freund-Michel et al., 2010). Moreover, *in vivo* treatment with anti-NGF blocking antibodies in animal models of pulmonary hypertension prevents the increased secretion of these inflammatory cytokines from diseased pulmonary arteries (Freund-Michel et al., unpublished data). Contribution of the TrkA receptor in these mechanisms remains to be determined, but our preliminary data support a role for NGF in the inflammatory mechanisms associated to pulmonary hypertension.

5.2 NGF, TrkA and tissue hyperresponsiveness

5.2.1 Asthma

A role for NGF was reported in airway hyperresponsiveness (AHR) associated to asthma, since pre-treatment with anti-NGF blocking antibodies reduces AHR in various animal models of asthma (Braun et al., 1998; de Vries et al., 2006; Glaab et al., 2003). In addition, AHR is observed after *in vitro* NGF pre-treatment of guinea pig (de Vries et al., 2001), ferret (Wu & Dey, 2006) or human bronchi (Frossard et al., 2005). AHR is reduced *in vivo* after administration of a pan-Trk receptor decoy in a mouse model of asthma (Nassenstein et al., 2006), or of the TrkA kinase inhibitor K252a in a guinea pig model of asthma (de Vries et al., 2006), thus showing involvement of the TrkA receptor in NGF-induced AHR.

5.2.2 Pulmonary hypertension

In the systemic circulation, neurotrophins play a role in the control of vascular tone (Caporali & Emanueli, 2009), and a role for NGF has been suggested in systemic arterial hypertension (Sherer et al., 1998). Neurotrophins and their receptors are expressed on pulmonary arteries (Ricci et al., 2000a), and their expression is increased in the lung of spontaneously hypertensive rats (Ricci et al., 2004a). A role for neurotrophins in the control of the pulmonary arterial tone was recently proposed, through activation of the $p75^{NTR}$ receptor (Xu et al., 2008). BDNF and NT-3 induce relaxation of porcine pulmonary arterial rings, through activation of the endothelial nitric oxide synthase (Meuchel et al., 2011). Suppression of TrkB or TrkC expression via siRNA as well as functional blockade of $p75^{NTR}$ suggest a role of both Trk and $p75^{NTR}$ receptors in these effects (Meuchel et al., 2011). In our ongoing studies in rat or human pulmonary arteries, we show that NGF does not induce rat or human pulmonary arterial contraction or relaxation by itself. However, NGF pre-treatment induces pulmonary arterial hyperresponsiveness to contractile agents such as

phenylephrine or prostaglandin F2α (Freund-Michel et al., 2010). Our preliminary data suggest that this effect may be due in part to activation of the TrkA receptors and increased intracellular calcium concentrations. These mechanisms are in accordance with the preliminary data recently described for BDNF and NT-3 by Prakash and co-workers (Prakash et al., 2010). Altogether, these results therefore suggest that neurotrophins, through activation of both Trk and $p75^{NTR}$ receptors, participate in both endothelial dysfunction and smooth muscle hyperreactivity observed in pulmonary hypertension.

5.3 NGF, TrkA and tissue remodelling

5.3.1 Asthma

Airway remodelling in asthma is characterized by a sub-epithelial fibrosis with an increased proliferation of fibroblasts and a thickening of the basement membrane, hypervascularisation, sensory hyperinnervation, oedema, and hypertrophy and hyperplasia of the smooth muscle layer (Bara et al., 2010). *In vitro*, NGF activates the TrkA receptor to induce migration of pulmonary fibroblasts (Kohyama et al., 2002) and regulation of extracellular matrix synthesis (Khan et al., 2002; Takahashi et al., 2000). These results therefore suggest a role for the TrkA receptor in NGF-induced airway sub-epithelial fibrosis *in vivo* (Hoyle et al., 1998). We also reported that NGF induces proliferation of the airway smooth muscle through activation of the TrkA receptor and may therefore participate to hyperplasia of the smooth muscle layer *in vivo* (Freund-Michel et al., 2006). Activation of the TrkA receptor by NGF also stimulates vascular cells from other origins than the lung to induce migration and proliferation of endothelial cells (Cantarella et al., 2002; Dolle et al., 2005; Lecht et al.,2010 ; Rahbek et al., 2005) as well as migration of vascular smooth muscle cells (Donovan et al., 1995; Kraemer et al., 1999). In addition, NGF stimulates angiogenesis *in vivo* through activation of the TrkA receptor (Cantarella et al., 2002; Caporali & Emanueli, 2009). NGF is also able to stimulate synthesis of angiogenic factors such as vascular endothelial growth factor (VEGF) from various cells through activation of its TrkA receptor (Nakamura et al., 2011). Altogether, these results suggest that activation of the TrkA receptor participates to NGF-mediated hypervascularisation in the lung (Hoyle et al., 1998).

5.3.2 Pulmonary hypertension

Vascular remodelling in pulmonary hypertension is characterized by increased proliferation, decreased apoptosis and increased migration of pulmonary vascular cells (Humbert et al., 2004). NGF-induced activation of the TrkA receptor contributes to migration and proliferation of vascular cells from other origins than the lung and stimulates angiogenesis (see paragraph above). Our recent results show that NGF induces proliferation and migration of pulmonary vascular cells through activation of the TrkA receptor (see paragraph 4.2 and Fig. 3) (Freund-Michel et al., 2010). Therefore, our findings support a role for NGF and its TrkA receptor in pulmonary vascular remodelling in this disease.

6. Therapeutic perspectives and conclusion

In regard of the different results presented in this review, NGF seems to play a major role in altered inflammatory, remodelling and reactivity processes occurring in pulmonary inflammatory diseases such as asthma or pulmonary hypertension. The TrkA receptor is involved in many NGF effects in the lung and targeting NGF or its TrkA receptor may be a new therapeutic perspective in these diseases.

Outside the lung, blockade of NGF is of therapeutic interest in other areas, in particular in pain therapy (Hefti et al., 2006). Humanized monoclonal antibodies against NGF or against TrkA, as well as small molecules acting as TrkA antagonists or as TrkA kinase inhibitors have been developed and are currently under investigation (Ma et al., 2010; Martin et al., 2011; McNamee et al., 2010; Ueda et al., 2010; Watson et al., 2008) **(Fig. 5**). In particular, tanezumab, a recombinant humanized monoclonal antibody against NGF, has been recently tested in clinical trials in osteoarthritic pain and chronic lower back pain and demonstrated good efficacy (Cattaneo, 2010; Lane et al., 2010). Such strategies may be applied in the near future to target NGF or its receptors in pulmonary inflammatory diseases such as asthma or pulmonary hypertension in which NGF and its TrkA receptor play an important role.

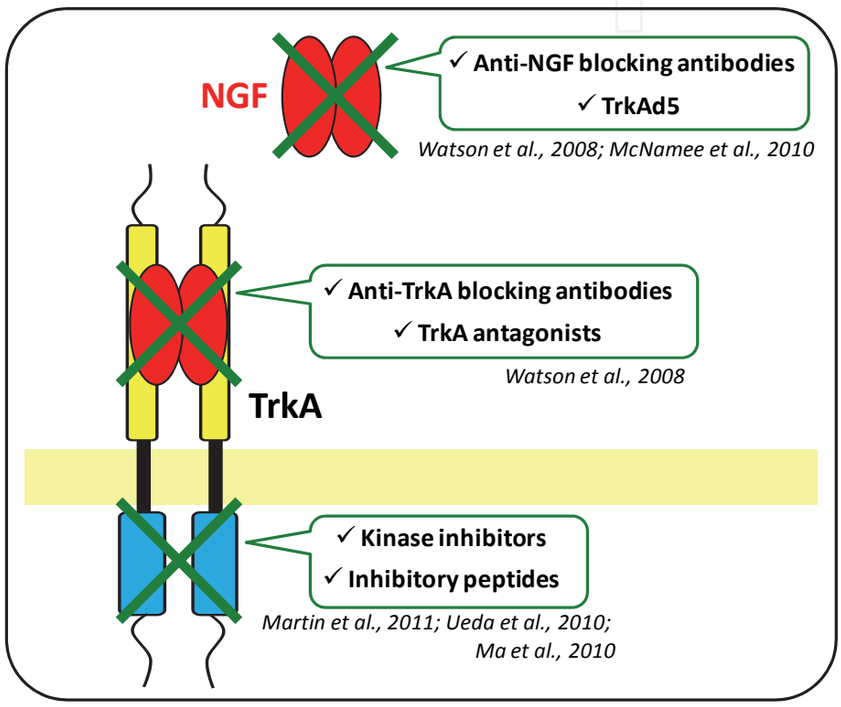

Fig. 5. Potential therapeutic strategies to target the TrkA receptor in pulmonary inflammatory diseases.
To trap circulating NGF and prevent its binding to the TrkA receptor, tools such as anti-NGF blocking antibodies or soluble chimeric TrkA receptors have been developed. Other tools have been developed to target the TrkA receptor itself, either by blocking NGF binding to its extracellular part with antagonists or anti-TrkA antibodies, or by blocking TrkA kinase activity with kinase inhibitors.

7. References

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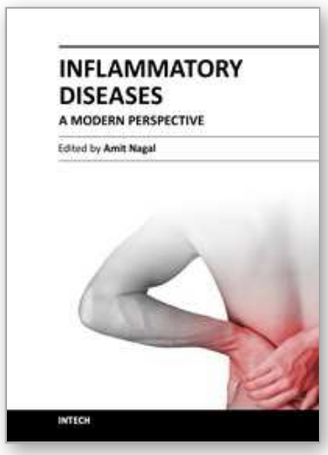

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