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REVIEW

# Role of p75 neurotrophin receptor in stem cell biology: more than just a marker

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**Abstract** $p75^{NTR}$, the common receptor for both neurotrophins and proneurotrophins, has been widely studied because of its role in many tissues, including the nervous system. More recently, a close relationship between $p75^{NTR}$ expression and pluripotency has been described. $p75^{NTR}$ was shown to be expressed in various types of stem cells and has been used to prospectively isolate stem cells with different degrees of potency. Here, we give an overview of the current knowledge on $p75^{NTR}$ in stem cells, ranging from embryonic to adult stem cells, and cancer stem cells. In an attempt to address its potential role in the control of stem cell biology, the molecular mechanisms underlying $p75^{NTR}$ signaling in different models are also highlighted. $p75^{NTR}$-mediated functions include survival, apoptosis, migration, and differentiation, and depend on cell type, (pro)neurotrophin binding, interacting transmembrane co-receptors expression, intracellular adaptor molecule availability, and post-translational modifications, such as regulated proteolytic processing. It is therefore conceivable that $p75^{NTR}$ can modulate cell-fate decisions through its highly ramified signaling pathways. Thus, elucidating the potential implications of $p75^{NTR}$ activity as well as the underlying molecular mechanisms of $p75^{NTR}$ will shed new light on the biology of both normal and cancer stem cells.

**Keywords** $p75^{NTR}$ · Neurotrophins · Signaling pathways · Stem cells · Cancer stem cells

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## Introduction

Since the discovery of pluripotent embryonic stem cells (ESCs), first isolated in 1981 [1], the ability of these cells to differentiate into three germ layers (ectoderm, mesoderm, and endoderm) and then into fully specialized cells [2] has opened many enticing perspectives in tissue regeneration and cell therapy. The comprehension of stem cell biology has become even more important with the discovery of cancer stem cells (CSCs) and their fundamental role in tumor development [3]. ESCs, adult stem cells, and CSCs share common features. They are all long-lived cells with the ability to renew through mitotic cell divisions and to differentiate into more specialized cell types. However, the stem cells are quite different in terms of potency, ranging from pluripotency in ESCs to multipotency, bipotency, and unipotency, with increasing degrees of commitment of transit amplifying/progenitor cells. Nevertheless, with the exception of hematopoietic stem cells, specific markers have not yet been identified. Studies of specific cell-surface markers are essential for distinguishing ESCs, adult stem cells, and CSCs from their destined-to-differentiate transit amplifying daughters to better understand mechanisms governing stem cell renewal and differentiation.

Among increasing prospective stem cell markers, the p75 neurotrophin receptor (p75$^{NTR}$, also known as NGFR or CD271) enriches the stem/progenitor subset in several models, presenting varying degrees of potency. p75$^{NTR}$ has been widely described for its signaling role as the common receptor for neurotrophins and proneurotrophins and, as such, p75$^{NTR}$ can exert a plethora of functions according to cell context [4, 5]. The aim of this review is to overview what is known about p75$^{NTR}$ in stem cell biology. Based upon the well-known and diverse signaling functions of p75$^{NTR}$, we also attempt to address its potential role in the control of stem cell proliferation and differentiation.

## Diverse functions of p75$^{NTR}$, the common receptor for neurotrophins and proneurotrophins

Since p75$^{NTR}$ was identified as a bona fide neural crest stem cell (NCSC) marker [6], it has been widely used to isolate putative stem cells from neural crest-derived tissues and its involvement in mesenchymal stem cell (MSC) differentiation along the osteogenic, adipogenic, chondrogenic, and myogenic lineages has been exploited. Nonetheless, p75$^{NTR}$ expression and function in vivo, as well as its underlying mechanisms in stem cell biology, have not yet been sufficiently addressed. In this chapter, we will briefly overview what is known about p75$^{NTR}$-mediated signaling, which may give us a clue about the role of p75$^{NTR}$ in stem cells.

p75$^{NTR}$ is the common receptor for all neurotrophins, which includes nerve growth factor (NGF), brain-derived neutrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4/5 (NT-4/5). Neurotrophins are generated from the enzymatic processing of their precursors (proneurotrophins). More recently, p75$^{NTR}$ has been reported to mediate the biological effects of proneurotrophins in several types of cells [7–9]. Nevertheless, proneurotrophins' in vivo activities still have to be demonstrated.

p75$^{NTR}$ is a 427-amino-acid transmembrane receptor containing an extracellular stalk domain, a single transmembrane domain, and a cytoplasmic domain. The presence of four cysteine-rich domains in the extracellular part of p75$^{NTR}$ affiliates it with the TNF receptor superfamily and is responsible for receptor conformation and ligand binding [10]. An *N*-glycosylation site and several *O*-glycosylation sites in the extracellular domain are implicated in the membrane targeting of the protein as well as in ligand binding [11]. The transmembrane domain consists of a unique helix, where the highly conserved cysteine C257 plays an important role in receptor dimerization, in conformational changes induced by ligand binding and in signal transduction [12]. The intracellular domain, which is highly conserved between species, does not have intrinsic catalytic activity, and it owes its signaling ability to its association with cytoplasmic partners through different regions. Three regions within the intracellular domain are important for p75$^{NTR}$ activity: (i) the chopper and (ii) death domain, the activation of which induces apoptosis [13], and (iii) the conserved SPV (tripeptide serine-proline-valine), which is a consensus sequence for Post-synaptic Disc-large Zona protein binding domains. The associated partners allow for assembly of protein complexes by acting as signaling platforms. The p75$^{NTR}$ intracellular domain is also subject to several post-translational modifications, such as palmitoylation [14] and phosphorylation, at several amino acid residues. For more specific details about p75$^{NTR}$, extensive descriptions of its structure and processing are reviewed in [15, 16].

p75$^{NTR}$ signal transduction pathways are extremely variable because they are strongly dependent on cell type, cell differentiation status, neurotrophin binding, availability of intracellular adaptor molecule availability, and interacting transmembrane co-receptors and post-translational modification expression [17]. This leads to divergent cellular responses, including cell survival [18], apoptosis [13, 19], neurite outgrowth and retraction [20], myelination [21], cell cycle regulation [22], cell migration and invasion [23, 24], and progenitor differentiation [25] (Fig. 1).

### Influence of co-receptors on p75$^{NTR}$ signaling

Formation of p75$^{NTR}$ dimers has a strong regulatory effect on the activation of receptor signaling [12, 26]. Nevertheless, different biological effects of p75$^{NTR}$ can be explained by the ability of p75$^{NTR}$ to cooperate with other receptors to form multimeric/heteromeric complexes. Indeed, apart from its interaction with specific tyrosine kinase receptors of neurotrophins (TrkA for NGF, TrkB for BDNF and NT-4/5, TrkC for NT-3), p75$^{NTR}$ participates in several signaling platforms by interacting with an increasing list of co-receptors, including sortilin (SORT1), Nogo receptor (NogoR), and LINGO-1 [27, 28] (Fig. 1). Interactions with co-receptors seem to be dependent on p75$^{NTR}$ cellular localization, the state of cellular differentiation, and its post-translational modifications [17].

p75$^{NTR}$ and Trk receptors can interact both in synergistic or antagonistic manners, and their association or mutual control has been extensively investigated [29]. The formation of a p75$^{NTR}$/Trk complex was shown to facilitate the affinity and selectivity of each neurotrophin for its Trk receptor ($k_d = 10^{-11}$ M), most likely by the induction of conformational changes in its intracellular and extracellular domains and exposing a high affinity site for association with neurotrophins [30]. Recently, a direct interaction

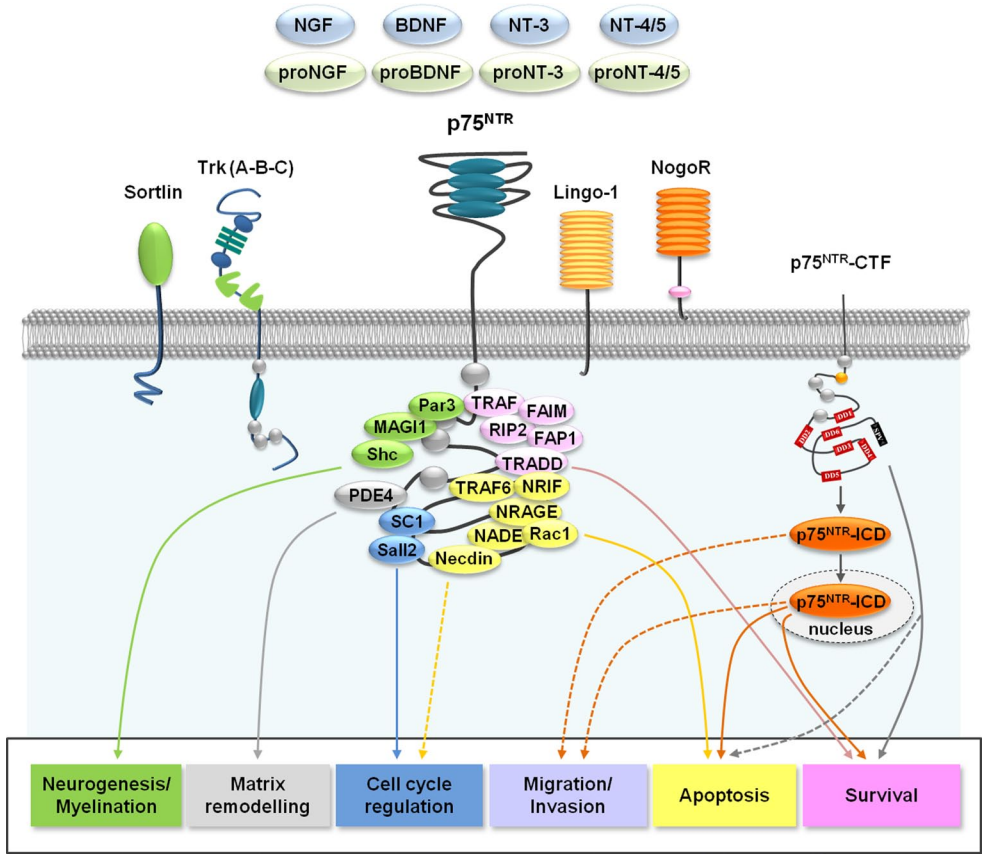


**Fig. 1** Schematic overview of $p75^{NTR}$ interactions. $p75^{NTR}$ can bind all neurotrophins and proneurotrophins, can dimerize, and can interact directly with Trk receptors, sortilin, Nogo-receptor, and Lingo1. The recruitment of intracellular proteins by $p75^{NTR}$ activates downstream signaling cascades, leading to different biological responses. $p75^{NTR}$ cleavage may also induce signaling mediated by the C-terminal fragment (CTF) or the intracellular fragment (ICD) of the receptor, generally leading to cell survival or apoptosis. ICD may be translocated to the nucleus to mediate its cellular responses (*dotted arrows* indicate that the exact molecular mechanisms leading to migration/invasion are unknown). In *yellow* are intracellular partners leading to pro-apoptotic signaling: *NRAGE* neurotrophin receptor-interacting MAGE homolog, *NADE* $p75^{NTR}$-associated cell death executor, *NRIF* neurotrophin receptor interacting factor, *Rac1* Ras-related C3 botulinum toxin substrate 1, *TRAF* TNF receptor-associated factor. In *pink* are partners leading to pro-survival signaling: *RIP2* receptor-interacting protein 2, *FAP1* Fas-associated protein 1, *FAIM* Fas apoptosis inhibitor molecule, *TRADD* TNF receptor-associated death domain protein. In *blue* are partners leading to cell cycle arrest: *SC1* Schwann cell factor-1, *Sall2* Sal-like 2; Necdin. In *green* are partners related to neurogenesis and myelination: *Par3* protease activated receptor 3, *MAGI-1* membrane-associated guanylate kinase with inverted organization; Shc. In *gray*, *PDE4* phosphodiesterase type 4, leading to cAMP degradation and matrix remodeling in Schwann cells

between $p75^{NTR}$ and TrkA has been demonstrated, even in the absence of NGF [31], and the possibility cannot be excluded that other proteins may be associated with this complex.

The $p75^{NTR}$/sortilin complex is known to induce cell death following proneurotrophin binding [32, 33]. Signaling pathways connected to the ternary complex proNT/$p75^{NTR}$/sortilin are poorly described. The cytoplasmic tail of sortilin has the potential to recruit specific protein partners to induce its own signaling and/or to facilitate $p75^{NTR}$-mediated signals.

Finally, the trimeric complex with NogoR and LINGO-1 receptors is known to bind to Nogo-66, myelin-associated glycoprotein (MAG), or oligodendrocyte myelin glycoprotein to inhibit neurite growth by activating RhoA [34–36].

## $p75^{NTR}$ signaling by the recruitment of intracellular partners

$p75^{NTR}$, like other members of the TNFR superfamily, does not have intrinsic enzymatic activity, and it owes its signaling to the recruitment of intracellular binding proteins, leading to the activation of different signaling pathways. These signaling pathways have been predominately established in neuronal models and in rat PC12 (pheochromocytoma) cells where, depending on the cellular context, they mediate survival, apoptosis, cell cycle arrest, myelination, or neurogenesis. There is a wide array of proteins that have been demonstrated to interact with the intracellular domain of $p75^{NTR}$ (Fig. 1). These include:

1. Neurotrophin receptor-interacting MAGE homolog (NRAGE) [37], NADE ($p75^{NTR}$-associated cell death executor) [38], neurotrophin receptor interacting factor (NRIF) [39], Ras-related C3 botulinum toxin substrate 1 (Rac1) and TNF receptor-associated factor 6 [40], leading to pro-apoptotic signaling mainly through activation of the JNK pathway;
2. TRAFs [41], receptor interacting protein 2 (RIP2) [42], Fas-associated protein 1 (FAP1) [43], Fas apoptosis inhibitor molecule (FAIM) [44] and TNF receptor-associated death domain protein (TRADD) [45], leading to pro-survival signaling through the activation of the nuclear factor-κB (NF-κB) transcription factor;
3. Schwann cell factor-1 (SC1), Sal-like 2 (Sall2), and Necdin, leading to cell cycle arrest [22];
4. Protease-activated receptor 3 (Par3), which is implicated in Schwann cell myelination [46];
5. Phosphodiesterase type 4 (PDE4), leading to cAMP degradation and matrix remodeling in Schwann cells [47];
6. Membrane-associated guanylate kinase with inverted organization (MAGI-1) [48] and Shc [49], both of which are involved in neurite extension.

### $p75^{NTR}$ proteolytic processing

The regulated proteolysis of $p75^{NTR}$ has largely been described in neurons. $p75^{NTR}$ undergoes extracellular cleavage by the metalloproteases ADAM17/TACE, releasing the ectodomain of the receptor to form a 28-kDa membrane-bound C-terminal fragment (p75-CTF) (Fig. 1). The p75-CTF is subsequently cleaved within the transmembrane domain by γ-secretase and gives rise to the soluble p75 intracellular domain (p75-ICD). The p75-ICD has been reported to be involved in cell death [50] or the survival [51] of neurons and in glioma cell invasion [52]. Whether these cleavages are regulated by neurotrophin binding or by co-receptors as well as their connection to $p75^{NTR}$ signaling are still a source of debate. It has been reported that in PC12 and HEK293 cell lines, TrkA activation increases $p75^{NTR}$ cleavage by ADAM17 [53, 54]. Several studies documented nuclear translocation of the $p75^{NTR}$-ICD fragment, suggesting a direct or indirect transcriptional activity of the receptor [55]. Although in the majority of cases $p75^{NTR}$-CTF was described as a transient form without signaling functions, this fragment has been more recently shown to be involved in the survival of breast cancer cells [56] and in promoting cell death in neurons when overexpressed in a form that cannot be cleaved to generate the ICD [50].

Despite the diversity of $p75^{NTR}$ signaling in adult cells, no specific signaling has been documented in a stem cell context. However, we can assume that in the case of stem cells, $p75^{NTR}$ is likely to function in a cell-context-dependent manner. Moreover, $p75^{NTR}$ activation has been shown to crosstalk with canonic signaling pathways involved in stem cell phenotypes, such as Notch and Wnt pathways. Indeed, NGF/$p75^{NTR}$ activation was described to be able to modulate the expression of hes1/5, which are target genes of the Notch signaling pathway, through NF-κB activation [57]. During axon regeneration, NGF regulates the activities of GSK-3β and ILK, in addition to PI3K and Akt [58]. By inactivating GSK-3β, NGF participates in the activation of the Wnt pathway, allowing for the stabilization of APC and β-catenin [59]. Moreover, Trk receptors directly phosphorylate β-catenin at the Y142 upon neurotrophin binding, driving β-catenin translocation to the nucleus [60]. Through β-catenin translocation, Wnt factors and NTs may regulate stem cell fate decisions by activating T cell-factor/lymphoid-enhancing-factor-driven gene transcription [61]. BDNF, for instance, seems to contribute to proliferation and neuronal and oligodendrocytic differentiation of NSCs in vitro by triggering the Wnt/β-catenin signaling pathway [62].

## Expression and potential roles of $p75^{NTR}$ in stem cells

Increasing amounts of data describe the expression of $p75^{NTR}$ in both stem cells and well-differentiated cells. In many cases, $p75^{NTR}$ has been used solely or in combination to identify stem/progenitor subsets with varying degrees of commitment, progressing from embryonic to adult tissues. In this chapter, we attempt to perform an up-to-date overview of both the expression and potential roles of $p75^{NTR}$ in stem cells according to their potency and germ layer origin (Table 1).

### $p75^{NTR}$ in embryonic stem cells

Embryonic stem cells are pluripotent stem cells originating from the inner mass of the blastocyst that have the dual ability to self-renew and to differentiate into all cell types within the embryo and the adult (Fig. 2). Some evidence concerning the role of $p75^{NTR}$ in human ESCs remains controversial. Schuldiner et al. [63] found that $p75^{NTR}$ is expressed in a human ESC line derived from human blastocysts, and its mRNA is down-regulated upon differentiation in monolayer culture. In the same cells, Pyle found only a transient or low expression of this receptor and supported the idea that BDNF, NT-3, and NT-4/5 neurotrophins sustain hESC survival through their binding to TrkB and TrkC receptors [64]. Nevertheless, whether the low amount of $p75^{NTR}$ detected in these cells might be implicated in the activation of TRK signaling pathways or in the neurotrophin response was not assessed, leaving the role of $p75^{NTR}$ unresolved.

**Table 1** $p75^{NTR}$ expression and functions in stem cells

| Cell type | Model | Plasticity | Origin | Ligand | Co-receptor | Functional outcome | Reference |
|---|---|---|---|---|---|---|---|
| Embryonic SC | Mouse | Totipotent | Blastocyst | NGF | TrkA | Proliferation | [65] |
| | Human | Totipotent | Blastocyst | | TrkC | Survival | [63, 64] |
| Neural crest | Human | Pluripotent | Neural crest | | | | [67] |
| Esophageal keratinocytes SC | Human | Multipotent | Ectoderm | | | | [136] |
| Laryngeal squamous SC | Human | Multipotent | Ectoderm | | | | [81] |
| Epidermal keratinocytes | Human | Multipotent | Ectoderm | | | | [82] |
| Hair follicle keratinocyte SC | Mouse | Multipotent | Ectoderm | | | Apoptosis | [85] |
| Corneal stromal and epithelial SC | Mouse | Multipotent | Neural crest | | | | [83] |
| Oral mucosa SC | Human | Multipotent | Ectoderm | | | | [84] |
| Dorsal root ganglion SC | Rat | Multipotent | Neural crest | | NogoR | | [76] |
| Gut SC | Human | Multipotent | Neural crest | | | | [77] |
| Sciatic nerve SC | Rat | Multipotent | Neural crest | | | | [72] |
| Enteric neural SC | Human, rodents | Multipotent | Neural crest | NT-3 | TrkC | Survival/ multipotency | [78, 79] |
| Dental pulp SC | Human | Multipotent | Ectoderm | NGF | | multipotency/ differentiation | [90] |
| CNS neural SC | Human, RAT | Multipotent | Ectoderm | NGF, NT-3, BDNF, proNGF | TrkC | Proliferation/ multipotency/ differentiation | [97–99] |
| Mesenchymal SC | Human, mouse | Pluripotent/ multipotent | Mesoderm | | NogoR, sortilin | | [65] |
| Bone-marrow SC | Human | Multipotent | Meso ectoderm | NGF | | | [107] |
| Adipose SC | Human, mouse | Multipotent | Mesoderm | | | | [109] |
| Testis SC | Human, mouse, rat | Multipotent | Mesoderm | NGF, NT-3 | TrkB | Differentiation | [154] |
| Skeletal muscle SC | Human | Multipotent | Mesoderm | BDNF | | Differentiation | [115] |
| Trachea epithelium SC | Mouse | Multipotent | Endoderm | NT-3 | | | [117] |
| Hepatic stellate SC | Human, rat | Multipotent | Endoderm | | | Differentiation | [122] |
| Melanoma CSC | Human | Multipotent | Ectoderm | NGF | | Selfrenewal/ multipotency | [128] |
| Oral squamous CSC | Human | Multipotent | Ectoderm | | | | [133] |
| Esophageal squamous CSC | Human | Multipotent | Ectoderm | | | | [136] |
| Breast CSC | Human | Multipotent | Ectoderm | | | | [146] |
| Hypopharyngeal CSC | Human | Multipotent | Ectoderm | | | | [148] |
| Neuroblastoma CSC | Human | Multipotent | Ectoderm | | | | [149] |

$p75^{NTR}$ expression has been found in numerous types of stem cells. In some cases, neurotrophins have been reported to be functionally implicated as indicated in the table. However, the precise functions of $p75^{NTR}$ in stem cells clearly remain to be studied

$p75^{NTR}$ was clearly found in the mouse embryo at the early blastocyst stage (3.5 days post-coitum, dpc) in Oct4-positive cells as well as in mouse ES cell lines [65]. Its expression persists in the inner cell mass of the blastocyst (4.5 dpc), while $p75^{NTR}$ transcripts are not present in trophoblast cells [66]. In particular, $p75^{NTR}$ is associated with mouse ESC proliferation upon NGF treatment through its interaction with the TrkA receptor [65]. Interestingly, primordial germ cells (unipotent stem cells) isolated from 11.5 dpc mouse gonads are found to be $p75^{NTR}$-negative but become $p75^{NTR}$-positive when dedifferentiated into pluripotent embryonic germ stem cells in vitro [65],

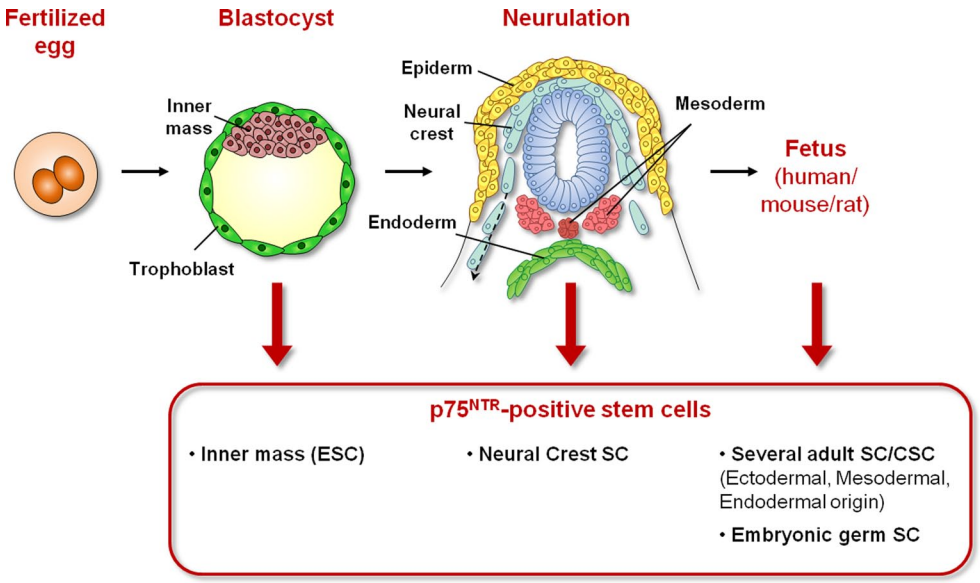


**Fig. 2** $p75^{NTR}$-positive stem cells are present in many cellular models with different degrees of commitment. The fusion of gametes and formation of a diploid zygote determines the establishment of a multicellular embryo. Cells from the inner cell mass of the blastocyst (ESCs) present $p75^{NTR}$ transcripts. $p75^{NTR}$-positive cells are present in multipotent migrating NCSCs (represented here during the neurulation stage) as well as in many fetal and post-natal tissues. It is worth noting that cell types other than neural crest-derived tissues present a subset of $p75^{NTR}$-positive stem cells, demonstrating a more primitive origin of these cells

suggesting that $p75^{NTR}$ is expressed by more primitive stem cells located high in the stem cell hierarchy.

Nevertheless, the close relationship between $p75^{NTR}$ expression and pluripotency thus far described indicates that neurotrophin signaling may be a key regulator of proliferation and survival in ESCs. Further studies are clearly needed to understand the precise dynamics of neurotrophin/$p75^{NTR}$ actions and the underlying mechanisms.

## $p75^{NTR}$ is a robust marker of neural crest SCs

It has been clearly established that $p75^{NTR}$ is a robust marker of NCSCs, as $p75^{NTR}$ has been successfully used to isolate NCSCs from fetal and adult tissues [67]. The neural crest is a transient population of multipotent stem cells arising at the lateral edge of the dorsal neural tube in vertebrates [68] (Fig. 2). These cells migrate extensively into the embryo before aggregating to form a vast array of cell types, including the neurons and glia of the peripheral nervous system, endocrine cells in the adrenal and thyroid glands, melanocytes, craniofacial cartilage and skeletal cells, among others [69–71].

Jiang et al. were able to generate functional NCSCs in vitro by FACS-sorting $p75^{NTR}$-positive cells from human ESCs whose differentiation was induced by stromal fibroblasts. These $p75^{NTR}$-positive cells readily form neurospheres in suspension culture, self-renew to form secondary spheres, and give rise to multiple neural crest lineages, including peripheral nerves, glial cells, and myofibroblastic cells. Importantly, these cells migrate and differentiate into neural crest derivatives when transplanted into developing chick embryos in vivo, demonstrating functional NCSC properties [6].

The persistence of $p75^{NTR}$ staining in stem cells originating from NCSCs in vivo was evaluated in E14.5 rat sciatic nerve tissue. Starting from post-migratory neural crest cells of the fetal peripheral nerve (which is thought to contain only glial precursors), a $p75^{NTR+}/P0^{-}$ (a peripheral myelin protein) fraction was identified as highly enriched in cells functionally indistinguishable from NCSCs in vitro. This subpopulation self-renewed in clonal assays and generated neurons, Schwann cells, and smooth muscle-like myofibroblasts [68, 72].

NCSC migration and fate are driven by environmental signals. For instance, the maintenance of an undifferentiated state as well as the persistent expression of $p75^{NTR}$ in NCSC are both supported by the combinatorial Wnt/bone morphogenic protein pathways [73, 74]. Neurotrophins act in combination with different factors to mediate different fates. Indeed, NGF, BDNF, or NT-3 act in concert with stem cell factor (SCF) to mediate cell death and melanocytic lineage through the $p75^{NTR}$ receptor, while the combination of FGF-2 and NT3 promotes expression of sympathetic neuroblast markers, and SCF and BDNF are involved in directing neural crest cells into a sensory neuron lineage [75]. These data emphasize the importance of the concerted action of neurotrophins and $p75^{NTR}$ in NCSC proliferation, survival, and differentiation. Based on the differentiation process, it cannot be excluded that neurotrophins may participate in NCSC migration and homing of $p75^{NTR}$-positive cells as well as in their specific differentiation once stem cells have reached their destination.

## $p75^{NTR}$ in adult stem cells

Adult stem cells are organ- or tissue-specific stem cells. These stem cells may be multipotent, bipotent, or unipotent, and maintain continuous cellular turnover to provide regenerative capacity in continually renewing tissues and

reparative capacity in post-mitotic tissues. In the adult, the presence of $p75^{NTR}$ characterizes various stem/progenitor cell types, such as bone marrow stem cells; muscle stem cells (satellite cells); liver stem cells (stellate cells); keratinocytes of the basal layer of the epidermis, of the corneal limbal epithelium and of squamous epithelia; and stem cells of the oral and esophageal mucosa. In general, $p75^{NTR}$ is considered to be the most specific marker of MSCs, which are endowed with adipogenic, osteogenic, and chondrogenic potential [65], and of stem cells of all neural crest-derived tissues [71] (Fig. 2).

*Ectodermal origin*

Several tissues originating from migratory NCSCs through a series of progressive restrictions in developmental fate have been shown to maintain a number of multipotent/bipotent undifferentiated cells bearing $p75^{NTR}$ expression. For instance, stem cells from dorsal root ganglion [76], adult gut [77], and sciatic nerve [72] have a subpopulation of $p75^{NTR}$-positive cells, displaying multipotency and sphere forming potential. Enteric neural stem cells isolated from the myoenteric plexus of both rodents and humans were shown to contain a rather homogeneous population of neural crest-derived cells that exhibit high proliferation, low apoptosis, and high expression of $p75^{NTR}$, as well as expression of neuronal precursor markers including Nestin, Ret, and Sox10 [78]. Differentiation of these cells in the enteric nervous system is driven by a combination of NT-3 and other neutrophic factors, through the up-regulation of TrkC and the concomitant down-regulation of $p75^{NTR}$ [79]. We can therefore infer that in these cells $p75^{NTR}$ may maintain the undifferentiated phenotype and survival of stem cells.

A $p75^{NTR}$-positive cell fraction has been found to be a useful stem/progenitor cell marker in many regenerative epithelia, such as esophageal keratinocytes [80], laryngeal squamous epithelial cells [81], and oral [25], epidermal [82], and corneal keratinocytes [83]. $p75^{NTR}$ expression is mainly restricted to the basal cell layer where keratinocyte stem cells are thought to reside [25]. In epithelial cells, $p75^{NTR}$ distinguished a relatively immature keratinocyte subset, slow-cycling in vivo and presenting a strong regenerative potential in vitro [80]. In particular, in human oral mucosal epithelium, $p75^{NTR}$-positive cells were shown to be Ki67-negative in vivo and to present a higher clonal growth potential in vitro, demonstrating the importance of this receptor for the maintenance of a stem cell pool through the induction of a quiescent state [25]. Importantly, the influence of neurotrophins on the activation of these quiescent $p75^{NTR}$-positive cells has not been tested. In human adult oral mucosa lamina propria, $p75^{NTR}$-positive stem cells are self-renewing cells that co-express Oct4 and partially express Sox2 and Nanog transcription factors [84]. $p75^{NTR}$ is also found to be involved in controlling the fate of murine keratinocyte SCs through cell–cell interactions, where $p75^{NTR}$-related signaling contributes to the control of hair follicle regression, most likely by driving apoptosis [85, 86]. A recent study has identified pluripotent $p75^{NTR+}/P0^{+}$ stem cells in the skin bulge that were shown to differentiate into all cell types in the adult [87]. Finally, NGF is able to drive healing in a model of corneal denervation by stimulating stem cell proliferation through the induction of $p75^{NTR}$, TrkA, and p63 (an epithelial stem cell marker) expression [88]. These results highlight the fact that NGF and $p75^{NTR}$ represent pleiotropic factors affecting stem cell self-renewal in regenerating epithelia.

$p75^{NTR}$ has been proposed to be a marker of neural crest-derived dental pulp stem cells. Deciduous dental pulp stem cells (DDPSC) have been characterized as a multipotent stem cell population with the ability to differentiate into mesodermal and neural cell lineages [89]. $p75^{NTR}$-positive DDPSCs have a high self-renewal capacity and the ability to migrate from the deciduous dental pulp tissues [90]. The adipogenic, osteogenic, chondrogenic, and neurogenic differentiation potential of $p75^{NTR}$-positive stem cells has been evaluated by their ability to form lipid droplets, mineralized nodules, and cartilage extracellular matrix [91, 92]. A study performed in 1996 by Luukko et al. found a direct correlation between the development of tooth innervation and the expression of neurotrophin receptors, postulating that $p75^{NTR}$ alone may mediate neurotrophin effects during the determination and differentiation of odontoblast and ameloblast cell lineages. $p75^{NTR}$ transcripts were first observed in the tooth germ during its transition from the bud to the cap stage in El6. One possible ligand for $p75^{NTR}$ could be NGF, which has been found in developing and adult rat teeth [93]. Another study detected NGF, proNGF, and $p75^{NTR}$ in rat incisors [94]. This indicates that $p75^{NTR}$ and its ligands are important for tooth development and are maintained in adult dental pulp stem cells.

$p75^{NTR}$ is also widely expressed in several cell types of the central nervous system (mainly derived from the neural tube), where neurotrophins and growth factors play an important role in the regulation of several biological processes at various stages of development [95] and after neural injury (glial cell damage, axonal degeneration, and traumatic injury) [96]. $p75^{NTR}$ is a specific marker defining a population of highly proliferative subventricular-zone stem or precursor cells responsible for neuron production [97]. In neuronal stem cells, $p75^{NTR}$ was shown to be essential for the induction of oligodendrocyte differentiation. BDNF mediates its effects on neurite differentiation by activating TrkB and $p75^{NTR}$, while NGF and NT3 were found to induce differentiation through an Erk1/2 signaling pathway

[97, 98]. In the same cells, proNGF/p75$^{NTR}$ signals reduced oligodendrocyte differentiation by the induction of cell cycle arrest [8], while truncated TrkC/p75$^{NTR}$ signaling is involved in neural differentiation [99]. p75$^{NTR}$ is rapidly downregulated in neurons during progenitors differentiation [100] while ectopical overexpression of p75$^{NTR}$ has been reported to induce cell death of GABA-ergic neurons in the dorsal telencephalon of chick embryos [101].

During neurodevelopment, p75$^{NTR}$-interacting proteins NADE, NRIF and SC-1 are co-localized with p75$^{NTR}$. The spatial and temporal ratio of NADE and NRIF seems to make individual neuroblasts or glioblasts more or less susceptible to p75$^{NTR}$-mediated apoptosis; SC-1 expression increases over time and seems to mediate p75$^{NTR}$-induced growth arrest during glial development [102]. Interestingly, after traumatic brain injury, NGF stimulates the expression of biomarkers associated with neural stem cell characteristics, such as Nestin [103], and induces stem cell migration and differentiation to developing and/or degenerating CNS regions. Altogether, these results present p75$^{NTR}$ as the core of complex signaling pathways driven by neurotrophins and Trk receptors. The neural stem cell system could therefore represent an ideal model to examine in depth how p75$^{NTR}$ can switch from one biological response to another.

*Mesodermal origin*

Mesenchymal stem cells (MSCs) are multipotent stromal cells present in adult marrow that have the potential to differentiate into lineages of mesenchymal tissues, including bone, cartilage, fat, tendon, muscle, and marrow stroma [104]. The staining of mesenchymal cells by anti-p75$^{NTR}$ antibodies was first reported by Thomson et al. [105]. In these cells, p75$^{NTR}$ acts as a key regulator of the maintenance of the undifferentiated status with a pivotal role in the regulation of MSC differentiation into osteogenic, adipogenic, chondrogenic, and myogenic lineages. To assess the effect of p75$^{NTR}$ on universal mesenchymal differentiation, Mikami et al. [90] constitutively expressed the human p75$^{NTR}$ protein in murine multipotent MSCs (C3H10T1/2 cells). p75$^{NTR}$ was shown to directly inhibit the differentiation of MSCs into multiple cell types, most likely through inhibition of transcription factors, including Runx2 and OSX, which are essential for osteoblast differentiation and for expression of the chondrogenesis marker Sox9 and the myogenic marker Myf5. In hMSC, activation of the NogoR-p75$^{NTR}$ complex leads to p75$^{NTR}$-mediated cell differentiation in a Trk- and neurotrophin-independent manner [90]. Moreover, increased expression of sortilin has been detected during early osteogenic differentiation where sortilin overexpression enhances mineralization by hMSC-derived cells after osteogenic differentiation, but it is not implicated in adipocyte commitment [106]. Thus, the differentiation promoting or inhibiting effects of p75$^{NTR}$ can be influenced by the absence or the presence of co-receptors. p75$^{NTR}$ is highly expressed in freshly isolated bone marrow mesenchymal cells when maintained in non-stimulated in vitro cultures and is rapidly down-regulated upon differentiation [107]. NGF was shown to drive bone marrow stem cell differentiation through the regulation of the Akt and MAPK signaling pathways [108]. Moreover, p75$^{NTR}$ distinguished a subset of multipotent adipose tissue-derived stem cells, which can be driven to differentiate into mature adipocytes, osteoblasts, chondrocytes, smooth muscle cells, and neuronal cells [109]. Further study showed that adipose tissue-derived stem cells, isolated with an anti p75$^{NTR}$ antibody, exhibited a high osteogenic differentiation potential [110].

Neurotrophins and their receptors are expressed in a differentiation-regulated and tissue compartment-regulated fashion during testicular and epididymal development in mice, rats, and humans [111, 112]. p75$^{NTR}$ is expressed at a very early stage of gonadal formation in the mouse (12.5 dpc), while no Trk receptor or neurotrophin immunoreactivity was detected [111]. Later in development, p75$^{NTR}$/NT-3/truncated-TrkB co-expression leads to epididymal smooth muscle cell differentiation in the mouse, but TrkA expression is connected to mesonephric tubule formation. In particular, an NGF gradient directly regulates proliferation and differentiation of Leydig stem cells and the peritubular myoid cell lineage [113], demonstrating that neurotrophins and their receptors play a pivotal role in the regulation of cell differentiation in the developing testis and epididymis.

p75$^{NTR}$ is displayed on human and rodent adult muscle stem cells in vivo (satellite cells) and is a key regulator of myogenesis, through BDNF binding [114, 115]. It should be emphasized that in all cases, p75$^{NTR}$ expression begins well before such embryonal structures become innervated, and the receptor is down-regulated when embryo myoblasts differentiate into myotubes [116].

*Endodermal origin*

The role of p75$^{NTR}$ and neurotrophin signaling in tissues of endodermal origin has been less thoroughly examined. The pseudostratified epithelium of the mouse trachea and human airways was shown to contain a population of basal cells functioning as stem cells and involved in tissue repair. A transcriptional profile performed by Rock et al. [117] noted that basal cells are enriched in *Ngfr* as well as in *Ntf3* (encoding for the NT-3 neurotrophin) transcripts, suggesting the possibility of an autocrine loop within this population.

Precursors of hepatic stellate cells, whose endodermal origin is still elusive [118, 119], express neurotrophins and their receptors, including p75$^{NTR}$ [120]. p75$^{NTR}$ has

been found to regulate transdifferentiation of hepatic stellate cells into myofibroblasts [120, 121], apparently without neurotrophin ligands or co-receptor interaction and through the activation of Rho signaling [122]. In particular, the intracellular domain of $p75^{NTR}$ is critical to quiescent hepatic stellate cells activation and hepatocyte proliferation, whereas $p75^{NTR-/-}$ hepatic stellate cells exhibit significantly reduced differentiation [122].

## $p75^{NTR}$ in cancer stem cells

Tumors usually are heterogeneous and comprise cells with different capacities to proliferate and differentiate. This cellular heterogeneity depends on the presence of so-called CSCs, which are defined as cells that can induce de novo tumor formation, self-renewal in vivo, and re-establish the cellular composition of the parental tumor.

Most of these cells have been isolated from whole tumor cell populations based on the expression of markers that characterize the stem cell compartment in the normal tissue of origin. In the context of cancer, several studies describe a tight connection between CSCs and $p75^{NTR}$ expression, especially in melanoma, squamous cell carcinoma, and breast cancer.

### *Melanoma*

Over the last decade, many authors have raised questions about the existence of a tumorigenic CSC population in melanoma. In 2005, Fang et al. [123] reported on a subpopulation of melanoma cells with characteristics of primitive progenitors for melanocytes that could give rise to a broad range of cell types. Since then, these cells have been studied extensively, even though the existence of human melanoma stem cells is still debated [124]. Indeed, the tumorigenicity of melanoma cells has been posited to be variable depending on the degree of immunodeficiency in recipient mice as well as on the extracellular environment into which melanoma cells are transplanted, leading to an overestimation of the tumorigenic potential of melanoma cells. Nevertheless, transplanted cells that are able to recapitulate melanoma heterogeneity are unlikely to be originating from non-tumorigenic or differentiated cells.

Melanocytes have a neural crest origin, and all the neurotrophins and their receptors are expressed when reverting to embryonic phenotype melanoma cells, although their expression is weak in normal melanocytes. $p75^{NTR}$/NGF signaling is known to be implicated in melanoma cell proliferation and migration [125] and has been associated with increased resistance of brain metastases [126, 127]. Starting from the fact that malignant melanoma, like normal melanocytes, derives from the neural crest lineage, Boiko et al. in 2010 found that melanoma $p75^{NTR}$-positive cells were able to initiate and maintain tumor growth in vivo in fully immunocompromised mouse models [T-, B-, and NK-deficient $Rag2^{-/-}\gamma c^{-/-}$ mice (RG) mice]. These cells were more metastatic and able to re-establish the original $p75^{NTR}$ expression heterogeneity of the primary tumor, confirming the multilineage potency of these cells. However, the discovery that a small $p75^{NTR}$-negative fraction was also able to generate tumors in these mouse models may imply that the tumor-initiating ability is not exclusively a feature of $p75^{NTR}$-positive cells [128] or that both $p75^{NTR}$-positive and $p75^{NTR}$-negative cells characterize melanoma stem cells at different stages. A phenotype switch appears to be a dominant phenomenon of melanoma stem cells and may be a major obstacle in their eradication [129–131]. Other groups confirmed that $p75^{NTR}$-positive melanoma cells have the capacity for self-renewal and sustain long-term tumor growth in vivo and that the incidence of $p75^{NTR}$-positive cells in patient biopsies is associated with poor prognosis for melanoma [132], indicating that $p75^{NTR}$ may represent a marker of a stem/progenitor cell subset within melanoma cells.

### *Squamous cell carcinoma*

In squamous cell carcinomas, $p75^{NTR}$ is known to play a pro-tumoral role. It is, for instance, associated with poor prognoses and a risk of local recurrence of oral cancers [133], where it is expressed in undifferentiated cell populations in oral leukoplakia and in oral squamous cell carcinoma (OSCC). This finding indicates that $p75^{NTR}$ could be a useful prognostic marker of OSCC [134]. $p75^{NTR}$ is correlated with perineural invasion in skin cancers [135] and is found in 50 % of esophageal squamous cell carcinomas (ESCC), where it is diffusely distributed in poorly differentiated tumors, suggesting that $p75^{NTR}$ is expressed in the actively proliferating, undifferentiated cell component of each tumor [136]. In ESCC specimens, p63, a keratinocyte stem cell marker, was confined mainly to $p75^{NTR}$-positive cells, which furthermore expressed lower levels of differentiation markers such as involucrin, cytokeratin 13, β1-integrin and β4-integrin [137]. $p75^{NTR}$-positive cells have the ability to self-renew and are resistant to chemotherapy, suggesting that it may be necessary for survival and maintenance of ESCC.

### *Breast cancer*

The involvement of neurotrophins in breast cancer is well documented. Indeed, breast cancer epithelial cells produce and secrete NGF, proNGF, BDNF, and NT4/5, which act on the same cells through an autocrine loop [138–140]. Normal and cancerous breast cells express both $p75^{NTR}$ and TrkA, but only cancer cells respond to NGF treatment with

enhanced proliferation, survival, and invasion [140–142]. $p75^{NTR}$ in breast cancer has been described as a marker of myoepithelial cells [143], and it has been used to identify a subset of cells with basal-like activity. Recent studies have shown that its overexpression increases the survival of breast cancer cells [144], or upon BDNF and NT-4/5 stimulation, recruiting the adapter TRADD to stimulate the NF-κB pathway and, consequently, cell survival [145]. A study by Kim et al. [146] showed that cultures derived from $p75^{NTR}$-positive clones of MCF-7, BT474, and BT549 cell lines as well as of primary tumor-derived cells, were able to recapitulate a pattern of heterogeneity similar to that of the global population, generating both basal-like and luminal-like compartments. In addition, $p75^{NTR}$-positive cells presented enhanced expression of miRNA 205, 221 and 222, which positively correlated with the maintenance of mammary epithelial progenitor cells in mice [146, 147].

*Other cancers*

Recently, $p75^{NTR}$ has been shown to define a stem cell-like population in hypopharyngeal cancer, exhibiting tumor initiation, self-renewal, and chemoresistance [148]. $P75^{NTR}$ is also expressed by neuroblastoma stem cells (SH-SY5Y neuroblastoma clone), as cells expressing $p75^{NTR}$ in association with c-kit and CD133 were found to display a highly clonogenic potency and a substantial plasticity [149].

## Concluding remarks

Despite the great interest engendered by stem cells, the manipulation of these cells has remained challenging because of the lack of specific markers to unequivocally define stem cells with different potencies and to distinguish them from transit amplifying cells in each cellular model. With the exception of the hematopoietic system, molecular mechanisms underlying stem cell differentiation are still poorly understood. Additionally, the potential functions of numerous prospective stem cell markers remain to be determined.

A close relationship between the expression of $p75^{NTR}$ and pluripotency has been noted by increasing amounts of data. $p75^{NTR}$ is noteworthy for its wide expression by several cellular models bearing different degrees of plasticity. Although it has been shown that $p75^{NTR}$ is expressed by ESCs, by migrating NCSCs, by adult stem cells originating from different germ layers and by an increasing number of CSCs (Table 1; Fig. 2), its real function in most of these cells remains enigmatic. The signaling pathways that are connected to $p75^{NTR}$ and the absence of catalytic activity in this receptor make it difficult to precisely define how this receptor acts. As stated above, $p75^{NTR}$ signaling can be modulated by its level of expression, dimerization, ligand-binding, interaction with co-receptors, intracellular partner recruitment and post-translational modifications. Thus, when considering the role of $p75^{NTR}$ in biological process, it is impossible to generalize a unique mode of action. Nevertheless, as was discussed above, $p75^{NTR}$ is implicated in the regulation of stem cell differentiation in several cell models, including mesenchymal, dental pulp, testis and bone marrow stem cells. This action could be achieved through the induction of a quiescent state, as documented in neuronal and hematopoietic stem cells or in breast cancer cells. We hypothesize that $p75^{NTR}$ could be a "fate decision" protein that enables stem cells to maintain their potency and to engage in differentiation according to the molecular and cellular context. Indeed, $p75^{NTR}$ is important for potency maintenance, and its expression is often down-regulated as a cell engages in a differentiation program. An example of how $p75^{NTR}$ may serve as a bi-directional switch in response to different stimuli is given by neuronal stem cells, where differentiation is strictly dependent on $p75^{NTR}$ ligand expression. In these cells, oligodendrocyte differentiation is induced by NGF and NT-3 and inhibited by proNGF in a $p75^{NTR}$-dependent manner [8, 98]. A mechanism facilitating $p75^{NTR}$ signal transduction could be its translocation in lipid rafts as a consequence of its phosphorylation at Ser304 by cAMP-PKA, as has been observed in cerebellar neurons [150]. Lipid rafts are cholesterol- and sphingolipid-rich microdomains in cell membranes that are believed to function in cellular signaling by concentrating or separating specific molecules in a unique lipid environment. Lipid rafts were shown to participate in the maintenance of ESC self-renewal [151] as well as in hematopoietic stem cell activation from quiescence [152].

The interest in $p75^{NTR}$ in stem cell biology also comes from the observation that developmental cells (especially neural stem cells) produce neutrophic factors that act on themselves and on surrounding tissues via autocrine and paracrine mechanisms [153].

Therefore, despite the physiological complexity and technological challenges, elucidating the potential influence of $p75^{NTR}$ as well as the underlying molecular mechanisms in a context-defined manner will shed new light on the biology of both normal and CSCs.

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