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CONCISE REVIEW

Nerve growth factor (NGF) and NGF receptors in mesenchymal stem/stromal cells: Impact on potential therapies

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Abstract

Mesenchymal stem/stromal cells (MSCs) are promising for the treatment of degenerative diseases and traumatic injuries. However, MSC engraftment is not always successful and requires a strong comprehension of the cytokines and their receptors that mediate the biological behaviors of MSCs. The effects of nerve growth factor (NGF) and its two receptors, TrkA and p75NTR, on neural cells are well studied. Increasing evidence shows that NGF, TrkA, and p75NTR are also involved in various aspects of MSC function, including their survival, growth, differentiation, and angiogenesis. The regulatory effect of NGF on MSCs is thought to be achieved mainly through its binding to TrkA. p75NTR, another receptor of NGF, is regarded as a novel surface marker of MSCs. This review provides an overview of advances in understanding the roles of NGF and its receptors in MSCs as well as the effects of MSC-derived NGF on other cell types, which will provide new insight for the optimization of MSC-based therapy.

KEYWORDS
cellular therapy, mesenchymal stem/stromal cell, nerve growth factor, P75NTR, TrkA

1 | INTRODUCTION

Mesenchymal stem/stromal cells (MSCs) exhibit fibroblastic morphology as well as self-renewal and multiple differentiation potentials.[1] The Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy has established the following

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minimal standard criteria for human MSCs: (a) must be plastic adherent (PA) under standard culture conditions; (b) must express CD105, CD73, and CD90 and lack surface expression of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR; and (c) must be able to differentiate into chondrocytes, osteoblasts, and adipocytes in vitro.[2] MSCs exist in various tissues, such as bone marrow (bone marrow-derived MSCs [BMSCs]),[3] and as other MSC-like populations, such as adipose tissue-derived MSCs (ADSCs),[4] skin-derived MSCs (SSCs),[5] Wharton's jelly-derived MSCs (WJMSCs),[6] umbilical cord blood-derived MSCs (UCBSCs),[7] placental-derived MSCs (PSCs),[8] and dental pulp stem/stromal cells (DPSCs).[9] However, biological characteristics of MSCs vary based on the in vivo environment as well as the isolation and expansion methods. Gene expression analysis has indicated that a considerable number of genes are differently expressed in MSCs derived from different origins. Cellular properties, including proliferation, multiple differentiation, migration and immunomodulatory activity, also vary among MSCs isolated from different tissues. Besides, MSCs tend to gradually lose their biological functions after in vitro expansion. Usually at passages 8 to 15, MSC begin to degenerate and show some cellular aging signs, such as larger cell size, reduced confluency, slower proliferation rate, attenuated multiple differentiation potential, and changes in molecular profiles.[10,11]

In fact, plasticity is a fundamental property of MSCs related to a whole sequence of cytological functions and even to the fate of MSCs.[12] A number of microenvironmental changes and molecular signaling pathways have been studied to elucidate the roles of growth factors, cytokines, and chemokines on the functions of MSCs. For example, transforming growth factor-beta (TGF-β) has been proposed to have a substantial effect on the properties of MSCs, including their proliferation, multiple differentiation, and immunomodulatory capacities.[13] Some cytokines that are widely used in the study of other cell types also display a certain regulatory action on MSCs, which has attracted increasing attention from researchers.

Nerve growth factor (NGF) is a member of the neurotrophic factor family that was first discovered by Levi-Montalcini in the 1950s. He conducted a study in which mouse tumors were transplanted into chicken embryos and produced NGF to stimulate the growth of sympathetic and sensory nerve cells and fibers.[14,15] An antiserum targeting this factor was able to destroy most of the sympathetic ganglia in various newborn mammals.[16] Later, its crucial roles in regulating the production of neuropeptides and neurotransmitters and the survival, growth, and differentiation of neurons in the peripheral and central nervous systems were revealed.[17-19] Moreover, NGF has displayed a superior nerve injury repair capacity in animal models[20,21] and in clinical trials.[22] A recent case report demonstrated that intranasal NGF administration improved the functional assessment and electrophysiological and clinical conditions of a patient with traumatic brain injury (TBI).[23] In addition, it was suggested that NGF also played significant roles in pain regulation via the stimulation of sensory and sympathetic nerve formation during the fetal period and elicitation of sensitization in both peripheral and spinal cord nerves during adulthood. NGF inhibitors could be used as new analgesics to prevent refractory chronic pain.[24-26] NGF has two membrane receptors: TrkA, a 140-kDa transmembrane tyrosine kinase that exhibits a high affinity for NGF and can be phosphorylated on tyrosine residues after binding to NGF,[27] and p75 neurotrophin receptor (p75NTR), also known as CD271, a 75-kDa glycoprotein belonging to the TNF receptor superfamily that shows a low affinity for NGF and can also bind to other neurotrophins.[28,29] The functions of NGF are not restricted to the nervous system, and numerous studies have shown that NGF has biological effects on MSCs.[30-32] The effects of NGF on MSCs are thought to be mediated mainly by the high-affinity receptor TrkA,[33] while the low-affinity receptor p75NTR is more likely to serve as a novel marker of MSCs.[34]

Significance statement

Mesenchymal stem/stromal cells (MSCs) have shown great promise in regenerative medicine, and their functions are regulated by various cytokines. This review provides an overview of the roles of nerve growth factor and its receptors in MSCs to potentially identify strategies to optimize the therapeutic effects of MSCs.

In this review, we focus first on the modulatory effect of exogenous NGF on MSC functions, the paracrine effect of MSC-derived NGF on other cell types, and the activation of the NGF/TrkA signaling pathway in MSCs. Then, we discuss the possibility of utilizing p75NTR as a surface marker for identifying MSCs as well as the cytological functions and superiority of the p75NTR$^+$ MSCs. Finally, we summarize the applications of the p75NTR$^+$ MSCs for MSC-based therapy in various diseases.

2 | EFFECT OF NGF ON MSCs

Previous studies have demonstrated that NGF exerts diverse cytological effects on neuronal cells, and such effects are now being observed in studies on MSCs (Table 1). Kolli et al investigated the effect of NGF on limbal stem cells (LSCs) and found that NGF and its receptors were expressed in LSCs, while NGF and p75NTR were downregulated throughout the differentiation period. In contrast, the expression of TrkA was variable but did not obviously decrease during the culture process. Blocking the action of NGF with an anti-NGF antibody led to reductions in DNA replication, colony-forming capacity and expression of the LSC markers *ABCG2* and *C/EBPδ* but to higher expression of the corneal epithelial cell marker *CK3*. Given these findings, the authors suggested that NGF played a key role in maintaining the stemness of LSCs.[35] In another study, Lu et al reported that the proliferation of BMSCs was promoted after treatment with NGF, as shown by a higher DNA content and increased hematoxylin and eosin (HE) staining.[36] However, Gronthos et al demonstrated that NGF did not support colony growth of MSCs under serum-deprived conditions, indicating that NGF was not able to initiate fibroblast colony-forming

TABLE 1 Effects of NGF on different types of MSCs

Cell type	Cell source	Passage number	Treatment	Results	Year	Ref
LSCs	Human	Not mentioned	Treated with an anti-NGF antibody	Exhibit reductions in DNA replication, colony-forming capacity and expression of the LSC markers but higher expression of the corneal epithelial cell marker	2019	35
BMSCs	Rabbit	Not mentioned	Treated with different concentration of NGF (0, 1.5, 3, 6 μg/mL for in vitro study and 0, 10 ng/mL for in vivo study)	Cells treated with 3 μg/mL NGF show highest proliferation and chondrogenesis abilities in vitro; cells treated with 10 ng/mL NGF show a better therapeutic effect on rabbits with cartilage damage in vivo	2017	36
BDSCs	Rabbit	P3	Treated with 3 μg/mL NGF	Display enhanced proliferation and chondrogenic differentiation abilities	2019	39
BMSCs	Mice	P3	Treated with NGF	Show greater osteoblastic differentiation and mineralization capacities	2018	40
BMSCs	Rat	P3-4	NGF gene modification	Enhance its neurogenic differentiation	2016	41
BMSCs	Rat	P3-5	Treated with different concentration of NGF (0, 50, 100, 200 μg/L)	Cells treated with 200 μg/L exhibit the most obvious reduction in apoptosis	2019	50
CSPCs	Human	Not mentioned	Treated with an anti-NGF antibody	Exhibit reduced matrix remodeling activity	2015	38
ADSCs	Human	P3-4	Treated with NGF encapsuled in chitosan nanoparticles	Enhance its neurogenic differentiation capacity	2019	42
UCBSCs	Human	Not mentioned	Treated with different concentration of NGF (0, 12.5, 25, 50 100 ng/mL)	Cells treated with 100 ng/mL NGF show the most enhanced neurogenic differentiation ability	2017	43
DPSCs	Human	P3	Treated with 100 ng/mL NGF	Enhance its neurogenic differentiation	2017	44

Abbreviations: ADSCs, adipose tissue-derived mesenchymal/stromal stem cells; BMSCs, bone marrow-derived mesenchymal/stromal stem cells; CSPCs, cartilage stem/progenitor cells; DPSCs, dental pulp-derived mesenchymal/stromal stem cells; LSC, limbal stem cells; MSCs, mesenchymal stem/stromal cells; NGF, nerve growth factor; UCBSCs, umbilical cord blood-derived mesenchymal/stromal stem cells.

unit (CFU-F) colony formation in MSCs.[37] Thus, NGF may promote MSCs proliferation through increasing its sensitivity to surrounding stimulating factors, rather than directly inducing the proliferation of MSCs.

After chondrogenic induction, NGF-treated BMSCs produced more GAG and type II collagen and expressed higher levels of cartilage-specific genes, such as *Aggrecan*, *SOX9*, and *COL II*, than untreated BMSCs in both monolayer cultures and 3D cultures. When used to repair damaged cartilage in rabbits, NGF-treated BMSCs showed a greater therapeutic effect than untreated BMSCs.[36] Furthermore, Jiang et al found that the expression of NGF was increased in osteoarthritic cartilage and in vitro-cultured chondrocytes exposed to interleukin (IL)-1β. NGF could serve as a chemokine to promote the migration of cartilage stem/progenitor cells (CSPCs). In addition, treatment with an anti-NGF antibody significantly affected the matrix remodeling activity of CSPSs.[38] This result was similar to the findings of Miao and colleagues, who suggested that NGF was better than TGF-β1 at enhancing the proliferation and chondrogenic differentiation abilities of MSCs.[39] Moreover, Cui et al reported that the ALP levels and calcium nodule formation ability were significantly enhanced in NGF-treated BMSCs compared to untreated BMSCs, suggesting that NGF promotes the osteoblastic differentiation and mineralization capacities of BSMCs isolated from mice with diabetes.[40] In addition, NGF can reportedly induce the neurogenic differentiation of a variety of MSCs, including BMSCs,[41] ADSCs,[42] UCBMSCs,[43] and DPSCs,[44] in vitro. Moattari et al proposed using NGF-treated MSCs to repair peripheral nerve injuries in rats. They demonstrated that better therapeutic effects were achieved with NGF in combination with MSCs than with MSCs alone, as shown by behavioral, electrophysiological, and histological assessments.[45] In fact, MSC differentiation is a complex process involving interactions between cells and extracellular environment. NGF may not serve as an inducer of MSC differentiation because it can promote the differentiation of MSCs into different cell types, including chondrocytes, osteoblasts, and neural cells. A more reasonable explanation is that NGF improves the responsiveness to differentiation inducers of MSCs, thus increase its differentiation tendency.

To elucidate whether NGF has an impact on BMSC angiogenesis and the possible mechanisms, Wang et al cultured BMSCs in Matrigel and treated them with different concentrations of NGF. They found that tube formation was significantly promoted in MSCs treated with 50 μg/L NGF and that this effect was associated with the enhancement of MSC proliferation but not with vascular endothelial growth factor (VEGF) expression.[46] In addition, it has been proposed that NGF acts as a pro-survival factor in various types of cells.[47-49] Wang et al found that NGF treatment increased the viability of BMSCs and suppressed hexanedione-induced apoptosis of BMSCs in vitro. They suggested that NGF could be used to prevent the apoptosis of BMSCs

to improve their transplantation into damaged tissues for regenerative therapy.[50]

3 | MSCs AND NGF: PRODUCTION AND FUNCTION

Cytokine secretion, which varies based on tissue origin, is regarded as one of the most important functions of MSCs.[51] Both BMSCs and ADSCs reportedly produce NGF, while BMSCs produce significantly more NGF than ADSCs.[52] Crigler et al found significant differences in NGF release in different MSC clones, suggesting that the expression of NGF was restricted to specific MSC subpopulations.[53] In addition, Peng et al induced WJMSCs into Schwann-like cells in vitro and found that differentiated WJMSCs were capable of producing neurotrophic factors, including NGF, and stimulating neurite outgrowth of PC12 cells.[54]

Bai et al reported that NGF could perfectly mimic the anti-apoptotic effect of conditioned BMSC medium and that this effect was abolished by intervention with an anti-NGF antibody, indicating that NGF was involved in the anti-apoptotic effect induced by BMSCs.[55] Interestingly, the concentration of NGF was higher in BMSC and neural stem cell (NSC) cocultures than in BMSC or NSC monocultures.[56] Thus, MSC transplantation may be an excellent tool for the local delivery of NGF into damaged tissues to promote the survival and repopulation of host neurons. Wang et al. injected BMSCs into 2,5-hexanedione-treated rats via their tail vein. After 4 weeks, they found that 2,5-hexanedione-induced neuronal apoptosis in the spinal cord was significantly attenuated due to an increased concentration of NGF.[57] Wu et al transfected the NGF gene into UCMSCs to improve the efficiency of NGF synthesis. Then, they intrathecally injected these transfected cells into the spinal cord to treat cystopathy in rats with diabetes and found that their voiding function improved as the NGF concentration increased.[58] In another study, Jo et al utilized BMSC transplantation to alleviate olfactory dysfunction. The study revealed that the expression of NGF and brain-derived neurotrophic factor (BDNF) was significantly increased at week 2 and slightly reduced at week 4. The thickness and composition of the olfactory epithelium were close to normal, and olfactory function was improved greatly. The authors suggested that BMSCs possessed therapeutic potential for olfactory dysfunction due to their paracrine actions, especially the secretion of NGF and BDNF.[34]

4 | SIGNALING TRANSDUCTION BY NGF AND TrkA IN MSCs

In neurons, TrkA is expressed on the plasma membrane with a extracellular ligand that could bind to NGF. Then NGF/TrkA signaling begins across into the intracellular cytoplasm and recruits those pro-differentiation and pro-survival signaling molecules, which are mainly signaling cascades including phosphatidylinositol 3-hydroxy kinase (PI3K)-protein kinase B (Akt), Ras-mitogen-activated protein kinase (MAPK), and phospholipase C gamma (PLCγ)-protein kinase C (PKC). As a result, the survival and differentiation of neural cells are enhanced.[33] (Figure 1A).

Although the NGF receptors TrkA and p75NTR are both expressed by MSCs, NGF binds more specifically to TrkA and then activates intracellular signaling pathways such as PI3K/Akt and MAPK/Erk (Figure 1B). Previous studies have demonstrated that Akt is involved in the growth and differentiation of MSCs.[59] Spontaneously, NGF promotes the proliferation of BMSCs by activating the PI3K/Akt signaling pathway. Treatment with NGF significantly enhances the Akt phosphorylation and proliferation of BMSCs, both of which are blocked by intervention with the specific PI3K inhibitor LY294002.[46] Bad is a downstream target of Akt that can be phosphorylated and inactivated by Akt,[60] while dephosphorylated Bad induces the apoptotic caspase-3 cascade.[61] NGF treatment significantly reduces the apoptosis of BMSCs and caspase-3 activity, and this effect is counteracted by the Akt inhibitor MK-2206. Thus, the protective effect of NGF against BMSC apoptosis may be achieved through the Akt/Bad pathway.[50]

Sirt1 is a member of the Sir2 family that plays roles in neuroprotection, cell senescence, apoptosis, and the inflammatory response by interacting with proteins in a variety of signaling pathways.[62] Recent research has indicated that Sirt1 activation induces the neuronal differentiation of BMSCs.[63] Zhang et al reported that NGF could induce the neural differentiation of DPSCs by increasing the expression of Sirt1. In addition, after treatment with NGF, phosphorylation of Akt and Erk is promoted in DPSCs, and this effect can be reversed by a Sirt1 inhibitor, indicating that the Akt and Erk signaling pathways may also be involved in the neuronal differentiation of DPSCs induced by NGF.[44] However, it is not clear whether the NGF-induced upregulation of Sirt1 expression occurs universally in MSCs or is restricted to DPSCs. Moreover, NGF can more robustly activate the PI3K/Akt signaling pathway than TGF-β1 during the process of MSC chondrogenesis.[39] Since the PI3K/Akt signaling pathway is commonly recognized to be involved in the chondrogenic differentiation of MSCs,[64] activation of the PI3K/Akt signaling pathway is important for the promotion of MSC chondrogenesis by NGF. In addition, the addition of K252a, an inhibitor of TrkA, can counter or even negatively affect NGF-induced BMSC osteogenic differentiation, indicating that TrkA is involved in osteogenetic stimulation by NGF.[40] Furthermore, Zheng et al constructed TrkA-overexpressing BMSCs and TrkA-shRNA-expressing BMSCs and used them to repair sciatic nerve defects in rats. The authors found that after 8 weeks, the TrkA-overexpressing BMSC group showed better nerve regeneration and functional restoration than the TrkA-shRNA-expressing BMSC group, suggesting that TrkA was involved in regulating the nerve regenerative potential of BMSCs.[65]

5 | P75NTR ACTS AS A NOVEL MARKER OF MSCs

In 1986, p75NTR was discovered by Johnson and his coworkers as the first NGF receptor[66] and was recognized as the sole NGF receptor

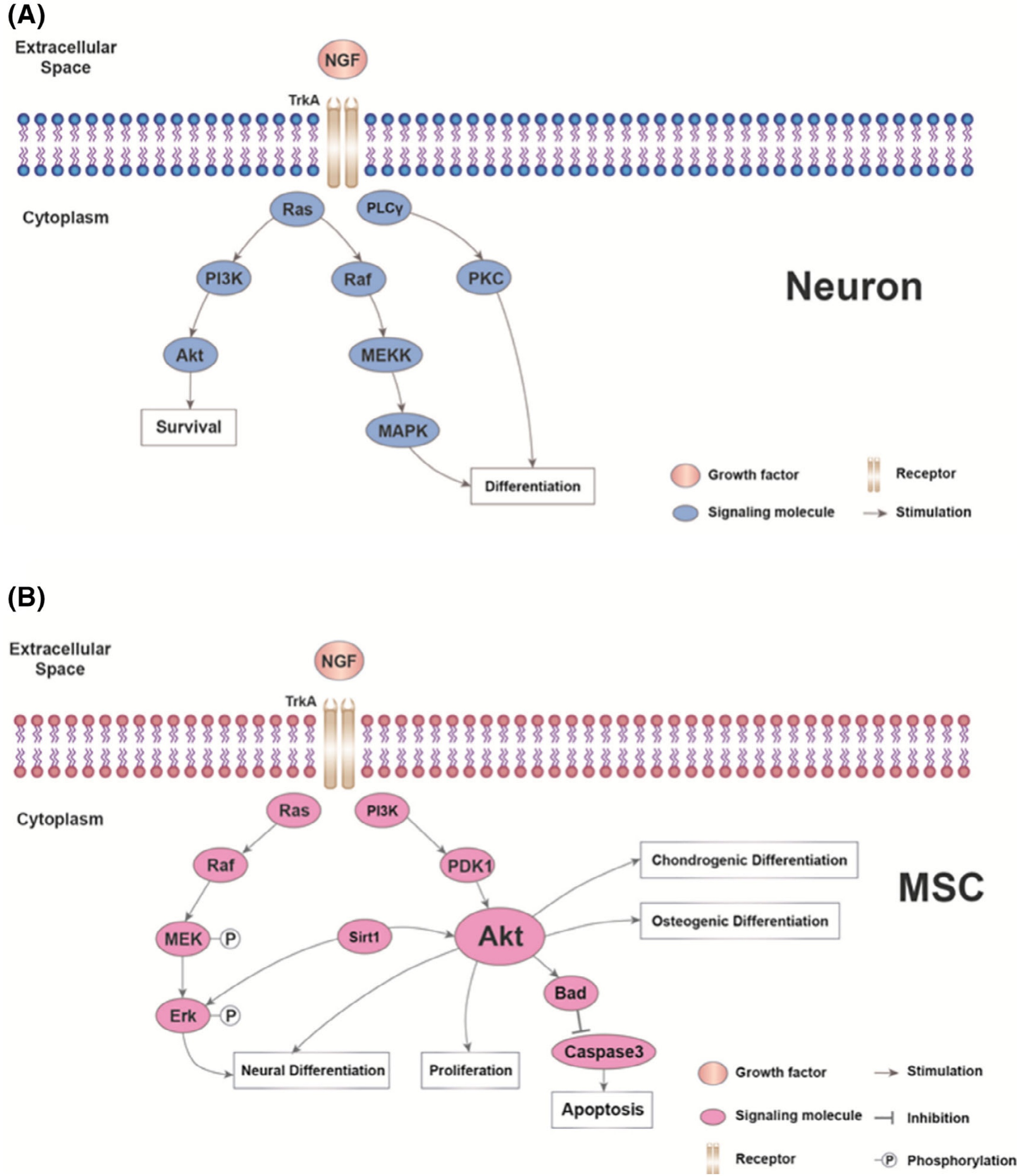

FIGURE 1 Overview of NGF/TrkA signaling pathways in neurons and MSCs. A, NGF binds to the extracellular ligand of TrkA and then actives PI3K-Akt, Ras-MAPK and PLCγ-PKC signaling pathways to promote the survival and differentiation of neurons. B, After binding to TrkA, NGF can activate the PI3K/Akt and MAPK/Erk signaling pathways in MSCs. Sirt is also involved in the activation of Akt and Erk, both of which can stimulate the neural differentiation of MSCs. In addition, the activation of Akt can promote the proliferation, chondrogenic differentiation and osteogenic differentiation of MSCs and prevent their apoptosis. MSCs, mesenchymal stem/stromal cells; NGF, nerve growth factor

until the identification of TrkA.[67] Under specific physiological conditions, p75NTR is able to induce cell death by interacting with cytokines, thus inducing the activation of nuclear factor kappa B (NF-κB) pathways[68] and the recruitment of cytosolic interactors to the death domain.[69] As a low-affinity NGF receptor, p75NTR has been reported to be involved in the regulation of the apoptotic effect of NGF. For example, since the expression of both p75NTR and NGF is increased in Alzheimer's disease, NGF/p75NTR is thought to be related to neuronal cell death.[70,71] These data demonstrate that p75NTR might play a negative role in neuronal cell survival, which is contrary to the effect of TrkA. However, it is also proposed that co-expression of p75NTR and TrkA results in enhanced neuronal cell survival.[72] In the presence of p75NTR, the affinity of TrkA to NGF is significantly increased (100-fold). On the other hand, the role of p75NTR in MSCs is relatively transparent. In 1993, p75NTR was first identified in human bone marrow stromal cells both in vivo and in vitro by Cottoretti and colleagues.[73] Later, Stro-1$^+$p75NTR$^+$ bone marrow stromal cells were shown to contain all of the assayable CFU-Fs after in vitro culture.[37] Since then, an increasing number of researchers have focused on the effects of p75NTR on MSCs. Traditionally, MSCs are harvested from

primary tissues due to their natural plastic adherence and are mixed with other adherent cells, such as macrophages and endothelial cells. Purified MSCs with better functional properties can be obtained through immunoselection based on specific MSC markers. In addition to the typical surface markers CD105, CD90, and CD73, other markers, including p75NTR, have also been identified to further characterize MSCs.[74,75] According to the literature, p75NTR is expressed by MSCs from different tissue sources, and the p75NTR$^+$ MSCs possess some unique properties (Table S1).

5.1 | Bone marrow-derived MSCs

In 1999, Pettenger et al found that cells with the ability to proliferate extensively and differentiate into multiple mesenchymal lineages could be isolated from human bone marrow, which was the first description of the isolation and characteristics of BMSCs.[3] Later, BMSCs were reported to express CD29, CD44, CD90, CD105, and lack expression of HLA-DR and c-kit.[76] Among the different MSCs derived from diverse tissue sources, BMSCs are one of the most common types used for MSC-based therapy and tissue engineering, and their characteristics have been extensively studied. It has been demonstrated that p75NTR is a specific marker for identifying BMSCs.[34] In 1993, Cattoretti and colleagues reported that an antibody against p75NTR labeled the majority of bone marrow stromal cells, which were positive for reticulin, collagen III and vimentin but negative for leukocyte, neural and endothelial markers.[73] In 2002, Quirici et al first isolated p75NTR$^+$ MSCs from the bone marrow and found that these cells showed greater colony-forming and expansion abilities and a greater potential to differentiate into adipocytes or osteocytes than PA MSCs.[77] In another independent study, Jones et al purified BMSCs by positive selection with D7-FIB-conjugated microbeads and negative selection with an anti-CD45 antibody and found that the D7-FIB$^+$CD45^{low} BMSCs were also positive for several unique markers, including p75NTR.[78] Bühring et al demonstrated that only the p75NTR$^+$ cells but not p75NTR$^-$ cells in bone marrow was positive for the MSC markers, including CD10, CD13, CD73, and CD105.[79] Due to its high expression on BMSCs, p75NTR can be used to isolate a homogeneous population of BMSCs with little hematopoietic contamination rather than a subpopulation of BMSCs only.[80-82] Specifically, Mabuchi et al proposed the use of p75NTR and CD90 to isolate extremely pure BMSCs, which exhibited ~200 000-fold higher CFU-F activity than unsorted bone marrow cells.[83]

Scheding and his coworkers indicated that MSCs in human bone marrow were highly enriched in p75NTR$^+$CD140a$^{low/-}$ cells, which expressed high levels of mesenchymal and multipotency genes and were able to generate nonadherent spheres with proliferation and full differentiation potential both in vitro and in vivo.[84-86] Jones et al revealed that in patients with osteoarthritis (OA), p75NTR$^+$ BMSCs were more likely to accumulate in femoral heads with bone marrow lesions, which were associated with enhanced cartilage damage and bone sclerosis.[87] Furthermore, p75NTR$^+$ BMSCs were found to reside adjacent to immature osteocytes and osteoblasts, indicating that they were osteogenically committed MSCs and potential therapeutic targets for OA or other bone-related diseases.[88,89]

Latifi-Pupovci et al demonstrated that p75NTR$^+$ BMSCs possessed much higher proliferation and migration capacities than PA BMSCs, indicating that the wound healing potential of p75NTR$^+$ BMSCs was stronger than that of PA BMSCs.[90] In a comparative study, Kuci et al reported that CFU-F activity was observed in only p75NTR$^+$ BMSCs, with no colonies being found in the p75NTR$^-$ cell fraction. Moreover, p75NTR$^+$ BMSCs secreted significantly higher levels of cytokines such as IL-10, MCP-1, IL-8, IL-1β, interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) than PA BMSCs. And p75NTR$^+$ BMSCs possessed a markedly stronger immunosuppressive capacity than PA BMSCs, as evidenced by an obviously greater inhibitory effect on the proliferation of T cells in a mixed lymphocyte reaction. Furthermore, researchers intravenously injected hematopoietic stem cells (HSCs) with p75NTR$^+$ BMSCs or PA BMSCs into immunodeficient mice and found that unlike PA BMSCs, p75NTR$^+$ BMSCs significantly improved the multilineage engraftment of HSCs and induced the differentiation of HSCs into myeloid and lymphoid cells.[91] In addition, Matsuoka et al found that the expression of HSC-supportive genes, including *IGF-2*, *Wnt3a*, *Jagged1*, *TGFβ-3*, *nestin*, *CXCL12*, and *Foxc1*, was significantly higher in lineage-CD45$^-$p75NTR$^+$SSEA-4$^+$ BMSCs than in other MSCs, suggesting that lineage-CD45$^-$p75NTR$^+$SSEA-4$^+$ BMSCs might play a key role in supporting HSCs in the bone marrow niche.[92] Although no differences between the trilineage differentiation abilities of unsorted BMSCs and p75NTR$^+$ populations have been reported,[90,91] evaluation of gene expression profiles has revealed that freshly isolated p75NTR$^+$ BMSCs express osteogenic, adipogenic and chondrogenic genes at higher levels than PA BMSCs, even after the third passage.[80]

5.2 | Adipose tissue-derived MSCs

In 2001, Zuk et al verified that human adipose tissue contained multipotent cells that were mesodermal or mesenchymal origin and could be maintained in vitro for extended passages and differentiate into adipogenic, osteogenic, chondrogenic and myogenic cells.[4] ADSCs coexist with endothelial cells and pericytes in the capillary and adventitia of larger vessels, which can be isolated from the stromal vascular fraction of fat tissue. A growing body of research indicates that ADSCs are pericytes due to their expression of pericyte markers CD146, PDGFR, NG2, and SMA.[93,94] Lin et al demonstrated that ADSCs were more likely to exist as CD34$^+$CD31$^-$CD104b$^-$SMA$^-$ cells in vivo.[95] However, ADSCs cannot be easily defined due to a lack of definitive cell surface markers,[96] even though many cellular markers have been investigated as possible ADSC markers.

It has been reported that the proportion of p75NTR$^+$ cells in adipose tissue is higher than that in bone marrow.[97] In 2007, Yamamoto et al attempted to purify ADSCs from mouse adipose tissue with an anti-p75NTR antibody and found that p75NTR$^+$ ADSCs were more prone to differentiate into adipocytes, osteoblasts, or neuronal cells than p75NTR$^-$ ADSCs, suggesting that p75NTR was a useful marker for

isolating ADSCs.[98] Similarly, Quirici isolated a p75NTR$^+$CD34$^-$ human ADSCs (hADSC) and demonstrated that the p75NTR$^+$CD34$^-$ hADSCs possessed higher CFU-F activity and higher proliferative and trilineage differentiative capacities[99] than PA hADSCs, and this finding was supported by a study by Calabrese et al.[100] In addition, Cuevas-Diaz Duran et al reported that over 90% of cultured p75NTR$^+$ hADSCs were positive for the MSC markers CD90 and CD105 but negative for the hematopoietic marker CD45. Moreover, the expression of p75NTR and some transcription factors related to cell self-renewal, such as *Sox2*, *Oct4*, and *Nanog*, in ADSCs decreased as the age of the donor increases.[101] Such observations were in agreement with the findings of Yamada et al in mouse ADSCs.[97] Based on these results, we suggest that p75NTR may be involved in in maintaining the stemness of ADSCs.

Kohli et al investigated the paracrine angiogenic activities of p75NTR$^+$ ADSCs and PA ADSCs and found that conditioned medium from p75NTR$^+$ ADSCs had a less robust effect on endothelial cell migration and tube formation than conditioned medium from PA ADSCs.[102] This study indicated that p75NTR$^+$ ADSCs may be favored seed cells for regeneration of avascular tissues such as cartilage. In fact, MSCs have both positive and negative actions to angiogenesis of endothelial cells. MSCs could secrete angiogenic factors, such as VEGF, fibroblast growth factor (FGF), and TGF-β, and antiangiogenic factors, such as activin A.[103] An examination of the secretion and gene expression levels of these factors in p75NTR$^+$ ADSCs and PA ADSCs may help to provide a clear explanation. Interestingly, Beckenkamp et al. reported that freshly isolated CD34$^+$p75NTR$^+$ ADSCs, but not CD34$^+$p75NTR$^-$ ADSCs, expressed high levels of CD140B, a molecule related to activated pericytes. Furthermore, in situ immunostaining of human adipose tissue revealed that p75NTR$^+$ cells existed in the inner region of the perivascular wall, such as the vessel lumen and endothelial lining, indicating that p75NTR$^+$ ADSCs were pericyte-like cells.[104]

5.3 | Dental pulp stem/stromal cells

In 2000, Gronthos et al isolated a clonogenic and rapidly proliferative cell type from human dental pulp, and these DPSCs were capable of forming dental/pulp complexes after transplantation into immunocompromised mice.[9] Later, other researchers confirmed that DPSCs could also differentiate into osteoblasts, chondrocytes, neurons, and adipocytes under specific conditions.[105] DPSCs are reported to express MSC-associated markers such as CD44, CD73, CD90, CD105, and CD146 in vitro.[106]

p75NTR is also identified as a biomarker of DPSCs.[107-109] Alvarez et al reported that p75NTR$^+$ cells accounted for 10.6% of human DPSCs and showed higher potential to differentiate into odontogenic lineages than cells expressing other markers, such as CD51/CD140a or STRO-1/CD146.[110] However, the potency of p75NTR as a stemness marker of DPSCs was challenged by Mikami and his coworkers. They isolated p75NTR$^+$ DPSCs and reported that p75NTR$^+$ cells exhibited greater clonogenic potential than p75NTR$^-$ cells but were less capable of differentiating into adipocytes and osteoblasts than p75NTR$^-$ cells.[111] Similarly, Yasui et al also revealed that p75NTR$^{(Low+)}$CD90$^{(High+)}$ DPSCs exhibited higher proliferation and multilineage differentiation potencies in vitro as compared with p75NTR$^{(High+)}$CD90$^{(High+)}$ DPSCs, indicating that p75NTR$^{(Low+)}$CD90$^{(High+)}$ DPSCs might represent precursors with high regenerative potential in dental pulp.[112] Above all, whether the multiple differentiation potential of p75NTR$^+$ DPSCs is greater than that of p75NTR$^-$ or PA DPSCs needs further research. Besides, the effects of p75NTR on other cellular functions of DPSCs also merit broader investigations.

5.4 | Skin-derived MSCs

The skin is the largest tissue in humans and consists of three layers known as the epidermis, dermis and subcutaneous tissue. In 2001, Toma et al found that MSCs were present in the skin and could proliferate and generate both mesodermal and neural progeny, including smooth muscle cells, adipocytes, neurons, and glia.[5] Tumbar et al demonstrated that SSCs were characterized by their localization in stem cell niches; expression of stem cell markers, contribution to wound repair and tissue regeneration in vivo; self-renewal, proliferation, and differentiation potential in vitro.[113] SSCs express surface markers similar to those expressed by BMSCs, including p75NTR.[114] The percentage of p75NTR$^+$ SSCs in the mouse dermis is 39.4%, and p75NTR$^+$ SSCs show higher proliferation and trilineage differentiation capacities than cells positive for other markers, such as CD44, CD90, and CD105.[115] In addition, Vaculik et al found that p75NTR$^+$ SSCs, but not CD73$^+$, CD90$^+$ or SSEA-4$^+$ SSCs, exhibited enhanced adipogenesis, osteogenesis, and chondrogenesis potential.[116] These findings indicate that p75NTR is important for determining the proliferative and differentiative capacities of SSCs.

It has been demonstrated that the number of p75NTR$^+$ SSCs decrease with donor age[117] and is significantly lower in patients with chronic skin ulcers than in healthy donors.[118] Furthermore, Zhang et al reported that overexpression of p75NTR in SSCs enhanced the proliferation, differentiation, migration, and antiapoptotic potentials in vitro. The researchers investigated the kinetic movement of p75NTR$^+$ SSCs in wound healing and found that the protein level of p75NTR in the epidermis was decreased at an early stage but increased promptly in the mid to late stages of the burn wound healing process, suggesting that p75NTR was involved in the re-epithelialization and remodeling of the epidermis in the mid-to-late stages.[119] Moreover, Iwata et al confirmed that p75NTR$^+$ SSCs proliferated and migrated to the sites of damage from 3 days after wounding and that the expression of TGFβ2, VEGFα, FGF2, EGF, PDGFB, and TGFβ1 in P75NTR$^+$ SSCs was higher than that in p75NTR$^-$ SSCs, indicating that the effect of p75NTR$^+$ SSCs on wound healing was achieved through not only differentiation but also paracrine action.[120]

5.5 | Other MSCs

Jones et al reported that the trabecular bone cavity contained abundant CD45^{low}p75NTR$^+$ cells with identical MSC phenotypes and

clonogenic potential, while the telomeres of $CD45^{low}p75NTR^{+}$ cells isolated from osteoarthritic or aged normal bone were shorter than those of the same phenotype of cells isolated from younger normal bone.[121] In addition, González-Garza et al reported that $p75NTR^{+}$ cells in the peripheral blood (PB) possessed self-renewal ability and expressed the surface markers CD73, CD90, and CD105 as well as the stemness genes *Nanog*, *Oct4*, and *Sox2*.[122] Iso et al extracted $CD45^{(low/-)}CD34^{+}p75NTR^{+}$ MSCs from human PB and found more of these cells in patients with acute myocardial infarction (MI) than in patients with stable coronary artery disease. The number of $CD45^{(low/-)}CD34^{+}p75NTR^{+}$ MSCs peaked on day 3, at which point it was positively correlated with the concentration of creatine kinase and then decreases until day 7, indicating that $p75NTR^{+}$ PB-MSCs were involved in the tissue repair process after acute MI.[123] However, Barilani et al demonstrated that the percentage of $p75NTR^{+}$ MSCs in fetal tissues such as umbilical cord blood, Wharton's jelly and amniotic fluid were lower than that in adult tissues such as bone marrow and adipose tissue,[124] indicating that p75NTR was an insufficient marker for isolating UCBMSCs,[125,126] WJMSCs,[127] and PSCs.[128]

6 | P75NTR AND MSC-BASED THERAPY

Hundreds of clinical trials using MSCs alone or in combination with other drugs to treat various diseases have been conducted.[129] The available data demonstrate that MSCs are safe for use in clinical practice since no direct associations among the application of MSCs and acute infusional toxicity, organ system complications, infection, death or malignancy have been detected.[130] However, some clinical trials failed to meet expectations for a number of reasons.[131] MSCs are a heterogeneous population that consists of different subpopulations with distinct phenotypes and functional properties.[132] The cellular heterogeneity of MSCs is hypothesized to have an impact on their functional characteristics and therapeutic potential.[133] As described above, $p75NTR^{+}$ MSCs are considered to possess better biological functions, such as higher proliferative, multilineage differentiation, immunoregulatory and cytokine secretion capacities, than $p75NTR^{-}$ or PA MSCs. Thus, it is quite promising to improve the therapeutic effect of MSCs on tissue damage by applying the $p75NTR^{+}$ MSCs (Table S2).

In 2011, Hermida-Gómez attempted to implant $p75NTR^{+}$ BMSCs or $p75NTR^{-}$ BMSCs into human articular cartilage sites for in vitro repair. They found that compared to $p75NTR^{-}$ BMSCs, $p75NTR^{+}$ BMSCs provided better filling of the chondral defect, better integration between the regenerated tissue and normal cartilage and a higher overall histological score, suggesting that $p75NTR^{+}$ BMSCs might have greater potency for cartilage regeneration.[134] In 2013, Mifune et al transplanted $p75NTR^{+}$ or PA BMSCs into cartilage defect sites in rats and revealed that $p75NTR^{+}$ BMSCs induced better cartilage regeneration than PA BMSCs, as evidenced by macroscopic, histological, and apoptosis analyses at week 8.[135] In addition, Yasui et al utilized DPSCs to repair murine calvarial defects and found that the $p75NTR^{(Low+)}CD90^{(High+)}$ subpopulation survived in the long term and promoted defect repair and bone regeneration.[112] Zhang et al reported that injection of $p75NTR^{+}$ SSCs into the dermal layer accelerated the convergence of skin wound healing.[136] In another field, Sadraddin et al proposed the use of $p75NTR^{+}$ MSCs to treat MI-induced ventricular arrhythmia in mice. They demonstrated that intramyocardial implantation of $p75NTR^{+}$ BMSCs immediately after the first MI had antiarrhythmic effects by significantly reducing the number of ventricular premature beats after the second MI.[137]

7 | PERSPECTIVE

MSCs have emerged as one of the most attractive seed cells for the treatment of degenerative diseases and traumatic injuries due to their potential to differentiate into various cell types.[3] Understanding the roles of NGF and its receptors in relation to the biological and functional properties of MSCs could be beneficial for developing prospective and effective MSC-based therapeutic strategies for regenerative medicine. NGF was reported to impact MSC properties, including their survival, proliferation, and multiple differentiation. More attention should be paid to the effects of NGF on other MSC functions, such as their immunomodulatory potential and paracrine activity. In addition, most related studies have focused on BMSCs, while other MSC-like populations, such as ADSCs, SSCs, DPSCs, and UCBSCs, have been investigated to lesser extent. Broader research on the effects of NGF on different types of MSCs could lead to comprehensively understanding the role of NGF in MSCs. In addition, the effects of NGF on MSCs in vitro have been confirmed, but its effects in vivo have been studied less often. For example, since NGF treatment could increase TrkA expression in vivo,[36] whether NGF has a potential role in regulating the MSC niche in vivo needs to be further investigated.

The effects of NGF and its receptors on MSCs may be related to the developmental origin of different MSC-like populations. The neural crest is a transitional structure in the embryonic development of *Vertebrates*. In the fourth week of embryo development, neural crest cells undergo extensive migration and evolve into different cells types and form various tissue components, including ectomesenchyme.[138-140] Thus, neural crest derived MSCs may express higher levels of NGF receptors. When stimulated by NGF, they may also display different functions. Besides, MSCs reside in different tissues that provide specific microenvironment for MSCs and facilitate them to maintain tissue homeostasis. MSCs from different tissue exhibit tissue-committed properties and the role of p75NTR in different types of MSCs may not be universal. Although most $p75NTR^{+}$ MSCs display greater proliferation ability, p75NTR may improve MSCs proliferation in varied degree. In addition, P75NTR is able to promote differentiation in BMSCs, ADSCs, and SSCs, but its role in DPSCs remain controversial. Although expression of p75NTR leads to reduced pro-angiogenic effect in ADSCs, whether it has the same effect on other types of MSCs need further investigation. Thus, a systematic comparative research on the effect of p75NTR on different types of MSCs is needed.

Although $p75NTR^{+}$ MSCs have shown great prospects in regenerative medicine, there are still some problems that need to be

addressed before their clinical application. Firstly, the effects of p75NTR on MSCs need to be further verified using more animal models and knock-out or knock-in models. Secondly, the relationships between p75NTR and other surface markers, such as nestin, leptin receptor, CD146 and Stro-1, warrant further study. Thirdly, the expression of p75NTR in MSCs is downregulated after in vitro culture,[92] and the optimization of their culture conditions or the development of novel biomaterials that could maintain MSC phenotypes would be conducive to improving the therapeutic effect of these cells. In addition, whether the expression of p75NTR could be maintained after MSC differentiation needs to be verified. Fourthly, the expression of p75NTR exhibits changes among different pathological conditions, which may provide clues to the repair mechanism of p75NTR$^+$ MSCs. For example, the expression of p75NTR in synovial membranes from OA patients are higher than that in normal synovial membranes, indicating that p75NTR$^+$ MSCs from bone marrow may be activated and then migrate through the vascular system into the joints during the cartilage degenerative process.[134] Fifthly, the signaling pathways mediated by p75NTR in MSCs remain unclear. Churchman et al revealed that p75NTR$^+$ BMSCs had greater transcriptional activity, particularly with regard to Wnt-related genes, than PA BMSCs.[141] Finally, p75NTR is a type I membrane molecule with an extracellular domain rich in cysteine residues that can shed into the intracellular space and bind with ligands in the surrounding area.[142] Since the MSC microenvironment differs substantially in different tissues, soluble p75NTR may be involved in regulating MSC functions by binding to various molecules, which contributes to its differential effects on different MSCs. Further studies on the potential molecular mechanisms are urgently needed.

8 | CONCLUSION

A growing body of research indicates that NGF plays an role in the survival, proliferation, and differentiation of MSCs. On the other hand, MSCs are also capable of secreting NGF to mediate the biological behaviors of other cell types. The regulatory effects of NGF on MSCs are achieved mainly through the interaction between NGF and its high-affinity receptor TrkA, leading to the activation of downstream genes, including Sirt1, PI3K/Akt, and MAPK/Erk, which are associated with the growth and differentiation of MSCs. More importantly, p75NTR is regarded as a novel surface marker for identifying MSCs with high proliferative, differentiation, immunomodulatory, and cytokine secretion potentials in different tissues. p75NTR$^+$ MSCs have been proven to result in better treatment effects than p75NTR$^-$ MSCs or PA MSCs and could thus be used to optimize the therapeutic capacity of MSCs.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

K.Z.: conception and design, collection and assembly of data, manuscript writing, conception of figures; Y.Y.: data collection, manuscript writing; G.T.: data collection; Z.S., Z.Y.: graphical design of figures and tables; X.L.: conception and design; X.S., S.L.: final approval of the manuscript; J.Z., Q.G.: conception and design, final approval of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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