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Targeting Matrix Metalloproteinases: A Potential Strategy for Improving Cell Transplantation for Nervous System Repair

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Abstract

Cell transplantation shows promise for repair of the injured nervous system, including spinal cord injury (SCI) and peripheral nerve injury (PNI). There are, however, still problems hampering these therapies moving from bench to bedside, and the methods need optimization. Three-dimensional (3D) cell culture systems are suggested to improve outcomes, bridging the gap between the in vitro and in vivo environments. In such constructs, cells are allowed to interact with each other and with the extracellular matrix (ECM) in 3D as they do in vivo. Transplanting cells in 3D constructs, rather than in suspension, is thought to promote cell survival and maintain important cellular behaviors. One such critical behavior is cell migration into and within the injury site. Understanding and controlling the migratory capability of 3D-cultured cells is therefore pivotal for developing better transplantation techniques. ECM remodelling can influence numerous cellular functions, including cell migration and matrix metalloproteinases (MMPs) are important enzymes for ECM modulation. Here, we discuss the idea of modulating MMPs to control cell migration in 3D culture systems, which can improve the therapeutic potential of cells transplanted in 3D.

Keywords

Olfactory ensheathing cells, 3D culture, migration, MMPs, extracellular matrix, spinal cord injury, peripheral nerve

Introduction

During the last three decades, cell transplantation therapies have emerged as promising strategies for repairing nervous system injuries, in particular spinal cord injury (SCI) and, more recently, large-gap peripheral nerve injury (PNI). Many cell types have been transplanted in animal models and human clinical trials and the proposed mechanisms by which they act can vary for the different sources, preparations, culture conditions, as well as how they are transplanted[1]. These cells include in particular glial cells, such as olfactory ensheathing cells (OECs), Schwann cells (SCs) and oligodendrocyte precursor cells (OPCs), as well as neural stem/progenitor cells (NSCs), and mesenchymal stromal cells (MSCs)[1–4]. Cell transplantation can lead to improved functional outcomes after SCI and/or PNI injuries as the transplanted cells can migrate and integrate into the injury site, including the glial scar, where they can ameliorate the inflammatory environment, promote neurotrophy, improve the extracellular matrix environment and aid the clearance of cell debris, all of which can support endogenous nerve regeneration[5].

Currently, cells are transplanted as a suspension; however, this delivery method causes great limitations. Many cells die, end up in the wrong place outside of the injury site, and may lose their phenotype and favorable cell behaviors, such as their ability to migrate long distances[2,6–9]. Three-dimensional (3D) cell culture systems have been suggested as a means to overcome these problems[2,6]. 3D culture systems allow cells to freely grow in all directions, and to

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interact and communicate with other cells as well as with the ECM[10,11]. Transplantation of cells in 3D constructs can also be used to direct the placement of cells into the injury site and improve cell survival[2,6,12,13], as 3D-cultured cells are more likely to act in accordance with their normal in vivo behavior[14]. 3D culture systems are also becoming an important tool for modelling cell behaviors in the laboratory in vitro[11,15].

The capacity for migration of transplanted cells is a key factor for cells to integrate within an injury site. While numerous aspects can influence cell migration, ECM composition and stiffness can play important roles[16,17]. Tissue stiffness has recently been mapped by atomic force microscopy (AFM) indentation[18–20]. Related studies demonstrate that changes of stiffness usually accompany different ECM compositions, which can alter cell behaviors in local tissue[16,21]. For example, retinal ganglion cell axons tend to migrate to lower ECM stiffness (softer) in vivo[22]. Several in vitro studies also suggest axons of neurons grow better on lower stiffness substrates[23–25]. Furthermore, the injured spinal cord has been reported to have lower stiffness compared to normal healthy spinal cord in rat (evaluated by a custom microindentation system[26] and AFM[27]) as well as in human (evaluated by ultrasound elastography)[28]. These reports suggest that softer ECM environments may mostly be desirable for nerve regeneration in SCI. Since ECM compositions can be altered following injury, future investigation into ECM modulation is important as this may aid the design of 3D cell constructs with ideal stiffness to match to transplantation site.

The ECM can be modulated; in particular, the degradation of ECM by proteolytic enzymes, such as matrix metalloproteinases (MMPs), is a major factor enhancing the capacity for cells to migrate in a 3D environment[29]. Here, we review the importance of the ECM in cell migration, especially in 3D culture systems. We also discuss the key roles of MMPs in ECM remodelling and cell migration. We suggest that modulating the activity of MMPs to control cell migration may be a promising complementary approach for transplantation therapies.

Cell Transplantation: Transition from 2D to 3D Culture Systems

In current cell transplantation therapies for SCI, cells in suspension are typically injected into multiple sites and at different depths[7–9]. However, the fragile and fluidic nature of the SCI site limits the ability for transplanted cells to migrate into and integrate within the injury site[30]. For example, after transplanting OECs and/or MSCs into SCI in rats, limited migration of the transplanted cells occurs as most of the cells die or are dispersed because of the injection pressure[30]. To overcome the limitations of injecting cell suspensions, experimental transplantation approaches using 3D cell constructs have started to emerge, targeting both SCI and PNI[31].

Using 3D cell preparations have demonstrated a range of improved functional outcomes when measured by various different factors. For PNI repair, transplantation of 3D cell constructs of SCs resulted in much better outcomes (evaluated with sciatic function index (SFI) and gait analysis) than transplantation of 2D conduits [32]. For SCI repair, transplantation of 3D constructs of glial cell types (such as OECs) into animal models has not yet been widely reported, however 3D constructs using other cell types (such as MSCs) have reported improved outcomes. For example, transplantation of 3D MSC constructs resulted in lower inflammation at injury site (such as reduced TNF-α, IL-1β, and IL-6), better axon regeneration and improved motor functional recovery compared to when cell suspensions were transplanted[33]. In vitro 3D models have also revealed changes that are consistent with improved outcomes when compared to 2D monolayers of cells. For example, when compared to 2D monolayers of cells, OECs seeded on 3D collagen scaffolds expressed higher levels of neurotropic factors (including nerve growth factor and brain-derived neurotrophic factor), which can improve neuronal differentiation[34]. Cells grown on 3D constructs also better preserve properties of OECs including survival, proliferation, morphology, and migration[34–36].

3D cell culture methods can roughly be categorized into scaffold/matrix-based and scaffold-free systems[37]. Scaffold-based methods use natural and/or synthetic materials for the cells to grow on, and have shown promise for enhancing the therapeutic potential of cell transplantation approaches. For example, conductive nanofibrous scaffolds can support survival and proliferation of transplanted OECs, improving repair of injured rat sciatic nerves[38]. However, scaffold-based systems have many limitations. Firstly, the biocompatibility of the transplanted scaffolds must be taken into consideration. It is possible that foreign materials and their degradation products can interfere with regeneration, induce inflammation or cause toxicity. Secondly, it is difficult to design a scaffold with desired cell density that can achieve organ-specific properties. For example, high seeding density of SCs onto hydrogel scaffolds can decrease the strength of the scaffolds, making them softer[39]. Furthermore, creating ECM-mimicking scaffolds that suit different cell types or precisely replicate the architecture of host tissues is difficult. While the use of scaffolds can aid cell growth, there are several obstacles to overcome, particularly as the inclusion of foreign or non-cellular components also increases the requirement for safety testing, leading to increased time and cost of therapy development.

To overcome these challenges, scaffold-free methods are currently being developed. Scaffold-free methods employ low adherence conditions, such as using gravity-enforced techniques or super-hydrophobic surfaces for cells to form 3D spheroids or aggregates[15,40–42]. Scaffold-free 3D culture methods can preserve cell-cell interactions and ECM production that mimic the in vivo microenvironment[15,43,44] and allow high cell densities[15,45]. Transplantation of MSCs in

scaffold-free spheroids has shown promise for repair in rodents with SCI and PNI, respectively[46,47]. The SCI study demonstrated higher secretion of protective proteins (such as cyclooxynenase-2 and glial cell line-derived neurotrophic factor) from cells in spheroids than in monolayer cultures[46]. However, the lack of vascular systems remains an unsolved issue for scaffold-free spheroid systems, particularly when the 3D cell constructs typically require culturing for several days. Unexpected cell necrosis can happen in long-term culture because cells in the construct rely on diffusion for oxygenation, nutrients and waste removal. We have recently developed a time-efficient 3D cell culture system termed the naked liquid marble (NLM), which allows rapid (less than 24 h) self-assembly of cell spheroids without artificial scaffolds/matrices[15]. In this system, cells form stable cell-cell contacts without the formation of a necrotic core and their robust construction enables easy manual handling for transplantation. Furthermore, cells cultured in the NLM system, including OECs, retain their ability to migrate[15,48,49]. To optimize this system, however, we next need to further enhance the migration of cells out of the 3D constructs to integrate with the host tissue. While there are numerous cell types being tested for transplantation therapies for neural repair, glial cells have gained particular interest with SCs and OECs being two of the most widely studied cells. While SCs and OECs share many similar properties, there are also distinct differences some of which make OECs more favorable than SCs. For example, OECs exhibit higher phagocytosis and trafficking capabilities, and produce lower pro-inflammatory cytokines compare to SCs[50]. Transplanted OECs can cause lower host astrocyte response and produce less inhibitory CSPGs in rat spinal cord than SCs[51]. In X-irradiated brain, OECs possess better migratory behavior and proliferation than SCs[52] and in X-irradiated spinal cord, OECs, but not SCs, can migrate extensively, accompanied with better phagocytotic and myelinating properties[53]. Due to the favorable properties of OECs, we will focus the following discussion of OECs while also considering other cell types.

ECM is for Cell Migration.

Cell migration is crucial for neural repair. For example, OECs in their natural environment of the olfactory nerve migrate ahead of emerging olfactory axons, acting as a guide for the axons as they extend from the nasal epithelium to the olfactory bulb[54,55]. OECs produce a range of growth factors, adhesion molecules and ECM components[55–57]. The growth-promoting properties of these and other glia make them good candidates for repairing injuries of the nervous system. For example, in rodents with SCI, transplanted OECs and/or SCs have been demonstrated to migrate into the injury site, correlating with axonal regrowth[58–61]. Some studies, however, have shown only limited migration of the transplanted glia[53,62]. Variation in outcomes is not surprising given the hostile microenvironment of injury sites. Cells within the 3D constructs are faced with the choice of remaining within the conducive environment of the construct versus the conditions of the host tissue and injury site. Therefore, successful integration of transplanted cells requires cell migration to be stimulated to encourage cells to migrate (1) out of the 3D construct and (2) into the host tissue (Fig. 1).

Cell migration is a fundamental cellular process that can be regulated by a variety of signalling networks[63], regulating cellular processes important for migration, such as cell-cell adhesion, cell-ECM adhesion, cytoskeletal protrusion/contraction, and proteolytic ECM remodelling[64,65]. Cell migration has been widely studied in 2D assays, while migration in 3D systems needs to be further investigated, in particular with focus on the roles of the ECM in migration. Scaffold-based 3D methods commonly use materials derived from natural ECM[66] or artificial ECM components[67,68]. In scaffold-free 3D systems, cells can secrete their own ECM, increasing the density of 3D cell structures and establishing more stable cell-cell and cell-ECM interactions[15].

ECM is a non-cellular macromolecular meshwork that supports a range of biological structures that, in addition to modulating cell migration, influences cell proliferation and inflammatory responses. ECM exists in almost all tissues and is constantly remodelled, and is composed of a large variety of molecules such as collagens, elastin, fibronectin, laminins, proteoglycans, and many other glycoproteins[69]. The composition of the ECM regulates the stiffness of tissues, which can significantly affect cell migration[16]. Therefore, successful integration of cells requires the cells to overcome both the ECM within the constructs and the ECM of the host tissues. If we could control ECM modulation, we may be able to improve cell migration out of constructs and into tissues. To date, very few studies have addressed this, but some findings have suggested that modulation of ECM may result in beneficial outcomes. For example, one study showed that 3D MSC constructs grown in hypoxia conditions leads to up-regulation of several ECM components (fibronectin, laminin, elastin, and glycosaminoglycan), resulting in better preserved stemness (stem cell phenotype), as well as improved attachment and integration on a tissue-mimicking substrate[44]. We have previously shown that OEC migration is closely related to cell density, with higher density improving migration through more cell-cell interaction[70]. What is not known, however, is the role of the ECM in regulating the migration of these cells. We have also shown that OECs in spheroids made from floating liquid marbles possess higher ability for migration than from sessile liquid marbles[71]. Perhaps differences in the ECM may partially account for such differences in the capacity for migration.

It is well known that differences in host tissue environments, including in the ECM of the host tissue, strongly influences cell migration and integration. For example, transplanted OECs, SCs or OPCs sometimes fail to migrate in the spinal cord of rodents[53,62], in other models such as X-irradiated rat spinal cords, transplanted OECs, but not

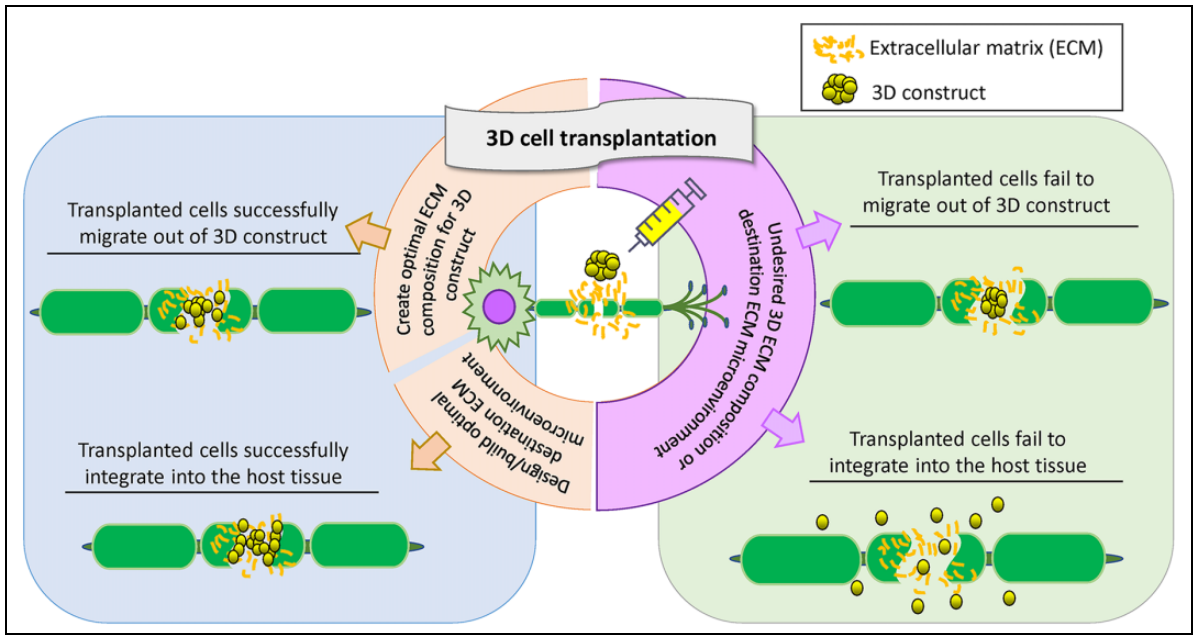

Figure 1. Modulation of ECM can encourage transplanted cells to migrate out of 3D construct and integrate into host tissue. While using 3D technique for cell transplantation therapy, transplanted cells to migrate out of 3D construct and migrate into the host tissue. Modulation of ECM compositions of 3D cells and design optimal ECM microenvironment can improve transplanted cells to migrate out of 3D construct and integrate into host tissue.

SCs, can migrate extensively[53]. It may also be that transplanted cells can also modify the ECM of the injury site, optimizing host environments for wound healing or nerve regeneration. Thus, host tissue environments vary by age, tissue types and whether an injury is present, and variation in ECM is likely a key factor regulating migration of the transplanted cells. The ECM composition is likely to affect cell migration as it is known that individual components can affect migration in in vitro models. For example, fibronectin can direct and promote migration of SCs[72–74], better than collagen I and laminin[75]. OECs exhibit better spreading and migration on laminin-coated surfaces than on two other ECM proteoglycans[76]. Fibulin-3, an ECM glycoprotein, can instead inhibit OEC migration and resultant OEC-mediated neurite outgrowth in vitro[77]. Moreover, the key inhibitory ECM component, chondroitin sulphate proteoglycans (CSPGs), has been reported to not only inhibit glial cell migration but also neural regeneration. With respect to injury sites where glial scars can form such as in spinal cord injury, CSPG is suggested as one of the constituents of glial scar formation which can negatively regulate neural regeneration[78,79]. CSPGs can inhibit differentiation and migration of OPCs in vitro[80] and astrocyte-produced aggrecan (a type of CSPG) is found to inhibit SC migration[81]. In contrast, enzymatic inhibition of CSPGs can improve OECs migration[82]. However, some cells can themselves modulate the inhibitory CSPG with transplanted OECs reported to reduce CSPGs (such as NG2 or neurocan) at spinal cord injured site and subsequently inhibit scar formation and improve axon regeneration in rats[83,84].

Hence, we need to understand how different cell types migrate in distinct ECM environments. This will allow us to (1) create the optimal ECM composition in 3D cell constructs, promoting migration out of the constructs, and (2) choose the best cell type for different host environments. It is also important to investigate key factors that can regulate and remodel ECM, which may allow further control of cell migration.

MMPs: Key Regulators of ECM Remodelling

MMPs are a family of endopeptidases that degrade ECM and have key roles in ECM remodelling. Most MMPs are calcium-dependent zinc endopeptidases, and can also target other non-ECM proteins such as growth factors, cytokines, receptors, as well as other MMPs. Thus, MMPs regulate many physiological and pathological functions[85,86]. Currently, there are 28 identified MMPs in vertebrates; 24 of these can be found in humans (including two equivalent forms that encoded by two distinct genes)[87,88]. There are two common classification systems of MMPs, based on structure and substrate specificity, respectively[89].

The structural classification is based on domain organization. This system classifies MMPs into four groups: minimal domain MMPs, simple hemopexin (Hpx)-containing MMPs, gelatin-binding MMPs, and furin-activated MMPs[89]. The basic MMPs contain a pro-peptide sequence, a catalytic domain with a zinc ion, a prolin-rich hinge region and a Hpx domain[90]. Only MMP-7 and MMP-26, the two minimal domain MMPs, do not have a Hpx domain and its associated

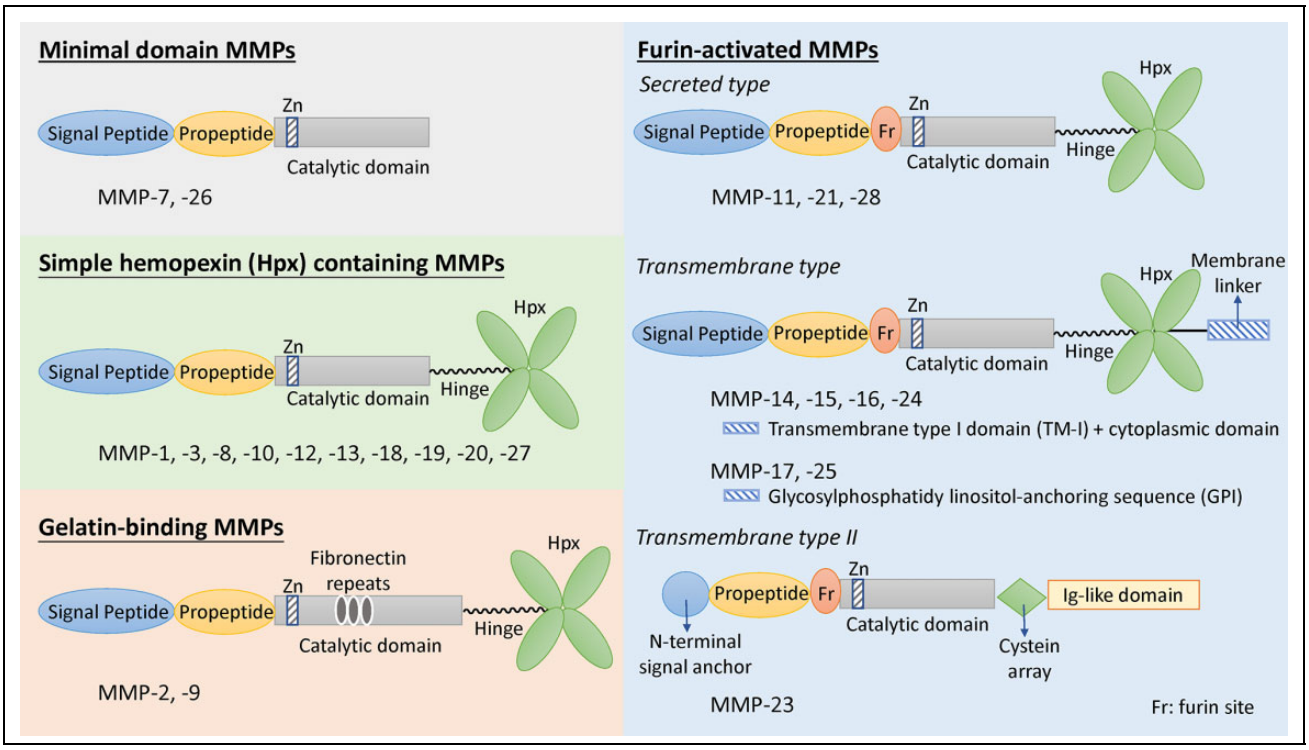

Figure 2. Domain structure of MMPs. Most MMPs share a similar basic structure: a signal peptide, a propeptide, a zinc-containing catalytic domain, hemopexin (Hpx) domain, and a hinge region. MMP-7 and MMP-26 are the smallest MMPs with minimal domain structure, lacking Hpx domain and hinge region. Gelatin-binding MMPs (MMP-2 and MMP-9) contain three fibronectin repeats in their catalytic domain. Furin-activated MMPs (including secreted MMPs, transmembrane MMPs, and one transmembrane type II MMP) contain a furin recognition site. Transmembrane-type MMPs contain a transmembrane domain and a cytoplasmic domain or a glycosylphosphatidyl inositol linkage (GPI). The transmembrane-type II MMP (i.e., MMP-23) has a signal anchor at N-terminal, and a cysteine array and an immunoglobulin (Ig)-like domain at C-terminal.

linker. Gelatin-binding MMPs includes MMP-2 and MMP-9, which contain three fibronectin repeats within their catalytic domain. Other MMPs exhibit a furin recognition site, which can be recognized and activated by furin-like serine proteinases. This group consists of several secreted MMPs, as well as two types of transmembrane MMPs, which are often referred to as membrane-type (MT)-MMPs. All MT-MMPs contain a membrane linker. This linker can be a transmembrane domain with a short cytoplasmic tail, or a glycosylphosphatidylinositol (GPI)-anchoring sequence. The other type of MT-MMPs (type II) have an N-terminal signal anchor, a cysteine array, and an immunoglobulin (Ig)-like domain (Fig. 2).

The other classification system, based on substrate specificity, divides the MMPs into six groups: collagenases (MMP-1, MMP-8, and MMP-13), gelatinases (MMP-2 and MMP-9), stromelysins (MMP-3, MMP-10, and MMP-11), matrilysins (MMP-7 and MMP-26), membrane-type MMPs (MMP-14, MMP-15, MMP-16, MMP-17, MMP-24, and MMP-25), and other MMPs (MMP-12, MMP-19, MMP-20, MMP-21, MMP-23A, MMP-23B, MMP-27, MMP-28). MMPs have also been found to target many non-ECM substrates such as cytokines and their receptors and can cleave pro-MMPs, which often leads to activation rather than degradation. The key ECM and non-ECM substrates of each MMP have been reviewed previously[91,92]. Many of the MMP functions are related to cell migration[93].

Potential of MMP Modulation in Nerve Repair

In addition to MMP-mediated modulation of cell migration, they also have a complex role in the nervous system. In SCI, up-regulation of MMP-1[94], MMP-2, MMP-9[95,96], and MMP-12[97] have been reported, while their inhibition is thought to attenuate destructive inflammation, neuropathic pain, neural apoptosis, and blood-spinal cord permeability[94,95,98]. However, MMPs have also been suggested to have importance for matrix remodelling during neural development, wound healing, and SCI repair processes[99]. MMP-mediated ECM remodelling is suggested essential in axon growth, regeneration, and neuromuscular junction development[100,101]. MMP-2 null mice have increased CSGPs and astrocytic scar at the injured site after SCI, which is accompanied with impaired functional[102]. The involvement of MMP-mediated pathways in peripheral nerve regeneration are also been reported. For example, MMP-12 mRNA level has been found to increase markedly after sciatic nerve injury, providing the preliminary evidence of MMPs in

peripheral nerve regeneration[103]. Also, a previous study determined that following a sciatic nerve crush there was a dramatic systemic change in numerous MMPs-related genes. Most of them (especially MMP-7 and MMP-12) were up-regulated, while MMP-28 was found to be down-regulated[104]. These results highlight that MMPs have a role in improvement of ECM remodelling and the generation of a desirable extracellular environment for nerve regeneration[104]. However, the changes in expression levels need to be carefully considered since an imbalance can exacerbate outcomes. For example, after PNI, elevations of not only MMP-3 and MMP-9, but also the tissue inhibitor of MMPs (TIMP-1) were found raising important concerns of the effect on ECM remodelling by MMP modulation[105].

There are also emerging studies demonstrating the potential of MMP modulation for improving behaviors of cell that are widely used for transplantation, such as OECs, SCs, and OPCs. OECs express MMP-2, MMP-3, and MMP-9, with MMP-2 suggested to be the dominant MMP[84]. When transplanted into the injured spinal cord, the OECs can then secrete MMP-2 in a rat model[106], which can degrade neurocan (a type of the CSGP)[84]. In SCs, MMP-2, MMP-7, and MMP-9 are expressed[107,108], with MMP-2 and MMP-9 demonstrated to be involved in TGF-β1-induced SC migration[108]. MMP-7 has been reported to improve SCs migration, which can further improve myelin sheath formation after PNI[107]. MMPs can also affect oligodendrocytes lineage cells with up-regulation of MMP-2 reported to aid the remyelination by OPCs via degrading CSPGs[109]; and MMP-12 can be secreted by oligodendrocyte lineage cells to regulate maturation and morphology of OPCs[110]. Accordingly, targeting MMPs may be an interesting strategy for improving behaviors of transplanted cells to enhance nerve repair.

Studies of MMPs in Glial Cell Migration

Migration is a known essential behavior for transplanted cells. MMPs are thought to primarily modulate cell migration via their proteolytic mechanisms and their ability to control glycolytic pathways. MMP-2, MMP-9, and MT1-MMP (MMP-14) are the most studied MMPs regarding effects on glial cell migration. MMP-2 modulates astrocyte migration, by focalizing at the migration front ("leading edge")[111]. TGF-β-induced up-regulation of MMP-2 and MMP-9 leads to enhanced SC migration[108]. Pharmacological improvement of MMP-2 and/or MMP-9 by natural products also induce SCs migration through MAPK pathways[112–115]. Conversely, inhibition of MMP-2 and MMP-9 can reduce migration of SCs[108] and OECs (on laminin and collagen substrates)[116]. Indeed, MMP-9 has been demonstrated to activate ERK1/2 and Akt in SCs to stimulate SC migration, with the hemopexin domain of MMP playing an important role in the cell-signalling response[117]. MT1-MMP is a key regulator of cell migration in general[29,118]. The proteolytic property of MT1-MMP can enhance the porosity of the ECM, enlarging ECM pores and thus creating migration paths[29,93,118]. Combined with other forces generated by adhesion molecules such as integrins, MT1-MMP can propel the cell nucleus and improve cell migration[29]. MMP-2, MMP-9, and MT1-MMP have also been suggested to play important roles in migration and neurotrophic properties in olfactory cells (including OECs)[119]. MT1-MMP is also involved in MMP-2 activation[120]. Furthermore, suppression of MMP-2 and MMP-9 by both genetic and pharmacological approaches in chick and mice has been shown to impair neural crest cell migration[121]; OECs have a neural crest origin[122] and thus these MMPs may regulate OEC migration during embryogenesis. In summary, MMPs have key roles in cell migration, in general increasing migratory behaviors. Thus, targeting MMPs is an interesting approach for increasing cell migration, in particular migration of transplanted cells out of 3D constructs.

Ongoing Trends and Future Perspective of the Usage of 3D Culture Techniques

To combine MMP modulation with transplantation of cells in 3D to repair the injured nervous system, understanding the properties of both the cells and the host tissue are important. For example, laminin and collagen are two typical ECM substrates in regenerating nervous system tissues. OECs possess good migratory capacity on both substrates; however, their migratory capacity can be completely blocked by inhibiting MMP-2, while inhibition of MMP-9 only partially attenuates migration[116]. Furthermore, OECs themselves can secret MMP-2, which can also degrade certain CSPGs. In addition to removing the inhibition of glial migration, degradation of CSPGs can expose permissive laminin, which can in turn promote neurite outgrowth[123]. These reports together support the potential of MMP-2 as an interesting target to enhance the therapeutic potential of transplanted cells such as OECs. For example, pharmacological up-regulation of MMP-2 in 3D constructs containing OECs, such as the spheroids created using the NLM method[15], or within the target injury area, constitutes a potential approach. Natural compounds such as the ginsenoside Rg1 has been reported to promote OEC migration, accompanied by MMP-2 up-regulation in vitro. In a rat SCI model, pre-treatment with ginsenoside Rg1 enhanced both motor function recovery of rats and histological results from rat spinal cord tissues after OEC transplantation[124]; perhaps, up-regulation of MMP-2 had a key role in this. Certain herbal extracts, such as Alpinate Oxyphyllae Fructus extract and its phenolic component protocatechuic acid, have been shown to improve SC migration accompanied with up-regulation of MMP-2 and MMP-9[115,125]. Thus, discovery of compounds that can modulate MMPs level is of high interest for many types of cell transplantation methods.

Conclusions

Cell transplantation, in particular of glial cells, constitutes a promising approach for treating nervous system injuries.

Moreover, transplanting cells in 3D, rather than as a suspension, can promote cell survival and integration, leading to better outcomes. One particular aspect of this therapeutic approach that needs improvement is cell migration out of the 3D construct and into the injury site. In this review, we suggest that modulating the activity of MMPs may achieve this. Thus, discovery of compounds that can stimulate MMPs may lead to better neural repair after cell transplantation.

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