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Engineering cell-derived extracellular matrix for peripheral nerve regeneration

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A R T I C L E I N F O

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A B S T R A C T

Extracellular matrices (ECMs) play a key role in nerve repair and are recognized as the natural source of biomaterials. In parallel to extensively studied tissue-derived ECMs (ts-ECMs), cell-derived ECMs (cd-ECMs) also have the capability to partially recapitulate the complicated regenerative microenvironment of native nerve tissues. Notably, cd-ECMs can avoid the shortcomings of ts-ECMs. Cd-ECMs can be prepared by culturing various cells or even autologous cells *in vitro* under pathogen-free conditions. And mild decellularization can achieve efficient removal of immunogenic components in cd-ECMs. Moreover, cd-ECMs are more readily customizable to achieve the desired functional properties. These advantages have garnered significant attention for the potential of cd-ECMs in neuroregenerative medicine. As promising biomaterials, cd-ECMs bring new hope for the effective treatment of peripheral nerve injuries. Herein, this review comprehensively examines current knowledge about the functional characteristics of cd-ECMs and their mechanisms of interaction with cells in nerve regeneration, with a particular focus on the preparation, engineering optimization, and scalability of cd-ECMs. The applications of cd-ECMs from distinct cell sources reported in peripheral nerve tissue engineering are highlighted and summarized. Furthermore, current limitations that should be addressed and outlooks related to clinical translation are put forward as well.

1. Introduction

Peripheral nerve injury (PNI) is one of the most common types of traumatic damage in the nervous system, affecting more than one million people worldwide every year with a high prevalence among younger individuals [1–3]. Currently, autologous nerve grafts have been considered the “gold standard” for peripheral nerve repair [4,5]. However, there are many drawbacks to autologous nerve grafts, such as limited availability of donor nerves and morbidity at donor sites [6,7]. It is imperative to develop new feasible nerve grafts as alternatives for the treatment of PNI. With the development of material science and tissue engineering, numerous artificial nerve grafts made by various synthetic and natural biomaterials have been devised [8–10]. Because of their low cell affinity and poor hydrophilicity, synthetic biomaterials are difficult to obtain neurotherapeutic functions comparable to natural biomaterials, and have therefore been gradually replaced by the latter [11,12]. It has to be mentioned that most of these natural biomaterials used to fabricate nerve grafts are only one or a few purified extracellular matrix (ECM) components. However, the various components in intrinsic ECMs have different physiological effects, and there are

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synergistic interactions between them. It is impossible to reproduce the complex regenerative conditions created by intact natural ECMs through mixing individual purified components [13–15]. This has motivated the applications of native ECMs themselves as biomaterial sources for peripheral nerve tissue engineering.

ECMs are the non-cellular constituents and form a three-dimensional network arranged in the intercellular space. They are complex and highly organized assemblies of macromolecules synthesized and secreted by cells, which are fundamental to the form and function of connective tissues [16,17]. ECMs constitute the microenvironment in which tissue cells live and play a key role in the regulation of various cellular behavior [18,19]. Cell-ECM interaction involves the synergistic effects of the chemical composition, structural organization, and biomechanical properties in ECMs, which enables ECMs to modulate essential physiological processes including the development, homeostasis, and regeneration of various tissues [20–22]. As naturally sourced biomaterials, ECMs have been continuously explored for decades in tissue engineering and regenerative medicine, and great progress has been made in constructing nerve repair grafts [23].

ECMs can be harvested from allogenic and xenogenic tissues or deposited by successive cell culture, which are tissue-derived ECMs (ts-ECMs) and cell-derived ECMs (cd-ECMs). In the field of peripheral nerve tissue engineering, acellular allogeneic nerves are typical td-ECM scaffolds. They preserve the native heterogeneous composition and inherent ultrastructure, therefore possessing tissue-specific functionality to some extent [24,25]. Acellular nerve grafts have been widely selected in the treatment of PNI and there are commercially available finished products that have been approved [26,27]. However, the clinical applications of acellular allogeneic nerves have been greatly restricted due to their unstable therapeutic effects and unavoidable inherent defects as td-ECMs, including potential disease transmission and host immunological rejection as well as batch variances [12,28,29]. ECMs derived from cultured cells emerge as promising alternatives for native ts-ECMs. Similar to ts-ECMs, cd-ECMs can also partially recapitulate the complex biological microenvironments established by native tissues [30]. However, cd-ECMs come into existence to mainly overcome the possible inflammatory or pathogenic risk associated with ts-ECMs. Cd-ECMs can be obtained from various cells or even autologous cells under strict cell culture criteria, and are readily to be amplified in large quantities *in vitro* [31,32]. The antigenic components in cd-ECMs can be effectively eliminated through mild decellularization, while better retaining their components and bioactivity [33]. In addition, cd-ECMs allow for specific tailoring for desired applications [34–36]. These render cd-ECMs significant advantages over td-ECMs. Therefore, cd-ECMs have received increasing recognition and are considered to be highly prospective biomaterials for peripheral nerve tissue engineering. This review comprehensively examines current knowledge about the functional characteristics of cd-ECMs and their mechanisms of interaction with cells in nerve regeneration, with a particular focus on the preparation, engineering optimization, and scalability of cd-ECMs. The applications of cd-ECMs from distinct cell sources reported in peripheral nerve tissue engineering are highlighted and summarized. Furthermore, current limitations that should be addressed and outlooks related to clinical translation are put forward as well.

2. Cd-ECMs vs ts-ECMs

In the field of peripheral nerve repair, research on cd-ECMs has been conducted much later than on ts-ECMs. The latter has been studied since the beginning of the 21st century and has achieved some clinical translation. In contrast, the applications of cd-ECMs in nerve repair have only gained attention in the last decade. For commercially available nerve grafts, the ts-ECMs mainly used are allogeneic nerves, whose primary sources are cadaveric or surgical waste tissues, which are inherently limited in supply [37]. Although these nerve tissues will undergo decellularization, the constraints of donor sources will still be exacerbated by the ethical and legal issues associated with harvesting human tissues and organs. Although there are no finished nerve repair grafts approved for marketing, xenogeneic nerve tissues of mammalian origin may be an option to address the lack of donors for ts-ECMs [38]. However, ethical concerns regarding animal welfare and human applications also need to be considered for the ECMs from animals. Notably, the ts-ECMs retain the neural microstructure consisting of basal lamina tubes, which are very dense, posing great difficulty for the infiltration of decellularization solutions and the elution of cellular debris [39]. The potential inadequate decellularization may raise the risk of adverse immune response and pathogen transmission [40]. Therefore, ts-ECMs often require rigorous processing to remove cellular components and reduce immunogenicity. However, the prolonged and complex decellularization will lead to significant damage to bioactive components and microstructures in ts-ECMs obtained, which may have a serious impact on their pro-regenerative capacity [41]. Cd-ECMs can be produced *in vitro* through cell-assembled ECM deposition of a fibrillar network. For peripheral nerve tissue engineering, source cells can be chosen from various types of stem cells or somatic cells as required and these can be extracted from the patients themselves. Moreover, milder, short-time, and few-step decellularizations can fulfill the cellular component removal requirements of cd-ECMs [42]. Cd-ECMs are readily to be acquired continuously *in vitro* due to the cells' expansion ability while maintaining them in pathogen-free conditions, and they have the potential to produce autologous ECM scaffolds and graft systems, which provides more possibilities to avoid undesired host response [43]. It has been suggested that due to the non-direct use of humans or animals, these cell-free matrices are associated with fewer ethical issues and safety concerns. However, in our view, although cd-ECMs only involve lab-grown allogeneic or xenogeneic cells, or even autologous cells, they also face similar ethical issues as ts-ECMs, which cannot be completely circumvented. Their research and translation should strictly follow ethical considerations and regulatory guidelines. The significant advantage of cd-ECMs over ts-ECMs is tunability. It is possible to control the cell culture process to achieve some desired output in terms of cd-ECM properties. Cd-ECMs can be customized by selecting cell sources, introducing genetic engineering, adjusting certain culture conditions, or adding specific external stimuli [44]. However, ts-ECMs are restricted in their capacity to tailor their bioactivity for specific applications beyond changing tissue sources.

Cd-ECMs can achieve very similar bioactive compositions to ts-ECMs, but it is difficult to make cd-ECMs with the adequate mechanical strength of the native counterpart nerves. Therefore, cd-ECMs do not have the ability of ts-ECMs to directly support bridging peripheral nerve defects. This is an important challenge for engineered nerve scaffolds when using cd-ECM biomaterials. Usually, cd-ECMs are required to be combined with synthetic biomaterials or crosslinked to tune and boost mechanical properties to meet the need for *in vivo* implantation [45]. However, it can be argued that cd-ECMs do not need to possess any of the physical properties, especially when they are intended for applications where matrix structural organization is unnecessary, such as repairing injured nerves in a hydrogel form. Moreover, whether for cd-ECMs or ts-ECMs, scalability issues are inevitably key challenges, which is the main reason for their slow progress in the last few years, especially for cd-ECMs [46]. In this regard, ts-ECMs are mainly constrained by the limited availability of donors. To date, the production of cd-ECMs is still on a laboratory scale. ECMs generated in cell cultures are relatively scarce, yielding micrograms to grams of materials from individual cultures [47,48]. More efforts need to be spent on the scale-up production of cd-ECMs and even their industrial manufacturing. Automated cell culture systems that can support ECM-producing cells in a high-throughput manner have been proposed [49,50]. This may be a feasible strategy to deal with scalability issues, which raises the prospect for clinical translation and commercialization of cd-ECMs. Furthermore, batch-to-batch variability is also one of the major concerns. The component types and proportions of ts-ECMs are not constant and may

vary with the age, gender, and health and disease status of individual sources [51]. In contrast, cd-ECM manufacturing systems have a better ability to continuously produce ECMs at high consistency [46]. However, attention should be paid to the passage number and senescence of source cells, as well as to the maintenance and monitoring of cellular characteristics, especially for stem cells. For both cd-ECMs and ts-ECMs, standardized production and quality control processes are essential to ensure product consistency and effectiveness.

Overall, cd-ECMs have some advantages over ts-ECMs, but they are not perfect as well (Table 1). The existence of cd-ECMs is not meant to be a revolutionary replacement for ts-ECMs, at least not at present, but more of a supplement and extension of ts-ECMs to enrich ECM-based biomaterial applications in tissue engineering and regenerative medicine, especially for peripheral nerve tissue engineering. The introduction of cd-ECMs brings a new track in the development of engineered nerve repair scaffolds, and also opens up the prospect of effective treatments for PNI patients.

3. Component characteristics of cd-ECMs

Although cd-ECMs from different source cells may have variable components, they, like ts-ECMs, are mainly composed of organic compounds, including fibrous proteins (such as collagens, elastin, and fibrillin), adhesive glycoproteins (such as laminin, fibronectin, and thrombospondin), glycosaminoglycans (GAGs, such as heparan sulfate, chondroitin sulfate, and hyaluronan), and other matricellular proteins, as well as a variety of inorganic compounds, which impart cd-ECMs biological activity (Fig. 1) [52,53]. These components can not only provide structural support and attachment sites for cells, but they are also the dynamic repositories of biological signaling molecules, facilitating the reciprocal dialogue with cells, which can modulate cell survival, proliferation, adhesion, migration, differentiation, and gene expression [54–56]. Therefore, ECMs play a vital role in the development and homeostasis of tissues and organs [57]. More importantly, they are indispensable constituents of the regenerative microenvironment, which can exert critical regulating effects for tissue repair following injury [58].

Collagens are enriched in all cd-ECMs [44,59]. They are essential structural proteins that are required for normal ECM assembly and organization, and constitute about 49 % of the total proteins of peripheral nerves [60–62]. Collagens are a superfamily of trimeric molecules composed of three identical triple helical α chains that define tissue structures, including up to around 30 identified subtypes. Among them, Collagen I, II, and III mainly participate in the composition of the epineurial ECMs [63,64]. Collagen IV, together with laminins and fibronectins, constitutes the perineurium of peripheral nerves [63]. Moreover, the inner and outer sheaths surrounding nerve fibers in the endoneurial tubes are mainly formed by various collagen fibers, including Collagen I, II, III, IV, V, and VII [65]. The ECMs derived from nerves are predominantly composed of Collagen I which is involved in fibril formation [66]. Collagens are involved in several mechanisms such as paracrine regulation of the cell behavior, and promotion of cell adhesion, proliferation, and differentiation, which play a significant role in supporting nerve regeneration [67,68].

Table 1
Comparison of the advantages and disadvantages of cd-ECMs and ts-ECMs.

	cd-ECMs	ts-ECMs
Advantages	Tunable composition for desired applications Lower decellularization difficulty Lower immunogenicity and pathogenicity Better batch consistency Autologous source cells	Retain composition and ultrastructure of native tissues Better mechanical properties Well-established preparation process
Disadvantages	Difficult to form native tissue ultrastructure Lack of mechanical properties Lack of standardized preparation process Scalability challenge	Limited availability of donors Higher decellularization difficulty Potential immunogenicity and pathogenicity Batch to batch variability

GAGs are also the major components of ECMs. They are carbohydrate polymer molecules that are covalently bound to glycoproteins in their native state to form inhibitory proteoglycans, such as chondroitin sulfate proteoglycans [69]. These molecules include heparan, keratin, chondroitin, dermatan, and their respective sulfates [70]. They link to a hydroxyl group of certain amino acids or core molecules which are also linked to hyaluronic acid, forming the side chains of proteoglycans. Due to their large size and negative charge, GAGs are thought to hinder neurite access to growth-promoting matrix molecules like laminin, thereby imparting axonal inhibitory activity to glycoproteins, which are implicated in the regulation of axon extension and guidance [71,72].

In addition, among the ECM noncollagenous molecules, the most important are laminins and fibronectins, which are the most widely studied ECM proteins in peripheral nerve regeneration [73]. Laminins and fibronectins together with collagens, as major components, participate in the constitution of most cd-ECMs [74].

Laminins are heterotrimeric glycoproteins consisting of one α, one β, and one γ subchain arranged in cruciform-shaped [75,76]. Eighteen isoforms of laminins have been described. α2, α4, β1, and γ1 laminin transcripts have been described in peripheral axon pathways [77]. Schwann cells themselves secrete laminin-211 (α2β1γ1) and −411 (α4β1γ1), which are distributed on the abaxonal surface of Schwann cells and participate in the formation of the basal lamina foundation [78]. Also secreted by Schwann cells, laminin-511 (α5β1γ1) is found in the basal lamina of peripheral nerves, which is associated with the organization of sodium channels within the nodes of Ranvier [79]. As the prominent component of the basal lamina, laminins are involved in cell differentiation, migration, and adhesion activities [80]. It is a ubiquitous constituent of the tight network of ECMs, which mediates cell attachment through ligand-receptor binding and provides adhesion sites for other ECM molecules, including nidogens, agrin, perlecan, fibulin, heparin, and sulfatides [81,82]. In peripheral nerves, laminins are the crucial bioactive part of the native ECM scaffold, which leads to pro-regenerative ability after injury [83].

Similarly, fibronectins have the characteristic of binding to cell surface receptors and other ECM components [84,85]. However, they mainly interact with collagen, fibrin, and heparan sulfate proteoglycans [86]. Fibronectins are large glycosylated proteins, which also act as vital ECM constituents [87]. This protein is composed of two subunits produced in the form of a disulfide covalently bonded dimer. In total, 12 isoforms for mice and 20 for humans have been described. In the nervous system, fibronectins are synthesized and secreted by Schwann cells and other non-neuronal cells, such as fibroblasts [88,89]. They participate in the formation of the fibrillar network of peripheral nerves along with collagens and laminins. Fibronectins can exert the functions of mitogen and chemoattractant, providing Schwann cells with a substrate conducive to their proliferation, migration, and differentiation [88,90,91]. Moreover, fibronectins can also serve as a substratum to support adhesion and outgrowth of regenerating axons [92,93]. The isoforms of fibronectins with the V region are considered to have superior neural repair potential. The V region contains a cell binding sequence (LDV, Leu-Asp-Val) that can be recognized by surface receptors of regenerating growth cones, such as α4β1 integrin [94]. Moreover, in the central cell-binding domain of fibronectins, the RGD tripeptide sequence (Arg-Gly-Asp) within the 10th Type III repeat can bind α5β1 integrin which is also expressed in newborn axons *in vivo* [95,96]. These provide a mechanistic basis for fibronectins to support axonal regeneration following nerve injury. It should be noted that, in addition to the major ECM components mentioned above, some other bioactive molecules, such as elastin, vitronectin, osteopontin, tenascin, and thrombospondin,

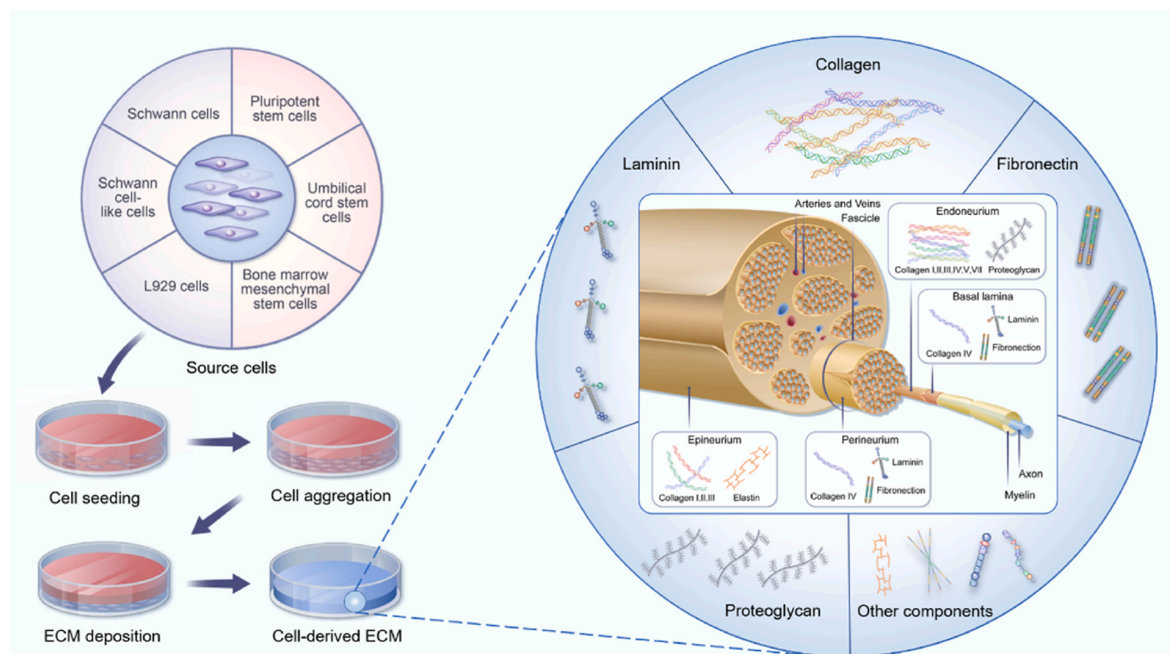

Fig. 1. The main components of cd-ECMs. In peripheral nerve tissue engineering, the main cell types used to prepare cd-ECMs are Schwann cells, Schwann cell-like cells, L929 cells, and a variety of stem cells, including pluripotent stem cells, umbilical cord stem cells, and bone marrow mesenchymal stem cells. ECMs from various source cells consist of a number of bioactive components, including mainly collagens, laminins, fibronectins, and proteoglycans, and may also include elastin, vitronectin, osteopontin, tenascin, and other components. These components are also involved in the composition of the ECMs of peripheral nerves, which have a great potential to provide excellent regenerative microenvironments for nerve repair after injury.

may be abundantly enriched in the matrices derived from various cell sources. These components can also exert important regulatory roles in the regeneration process after PNI [97].

4. Functional properties and mechanisms of cd-ECMs

ECMs play important roles in the developmental stage of nerve tissues and the regeneration stage after nerve injury [98]. Cd-ECMs preserve the functional properties of their intrinsic microenvironment and have specific regulatory capacity [99]. Compared with ts-ECMs, cd-ECMs are more commonly considered an *in vitro* niche. Because of their promising biological characteristics, cd-ECMs have the capacity to serve as a suitable template for establishing a dynamic regenerative microenvironment [100]. For peripheral nerve regeneration, Schwann cells are definitely the first to be mentioned as source cells. The ECM secretory function of Schwann cells plays a key role in the formation of peripheral nerve ECMs. The basal lamina is even formed almost entirely by ECMs deposited by Schwann cells [101]. Moreover, following nerve injury, various bioactive factors secreted by Schwann cells are also critical in supporting spontaneous regeneration of peripheral nerves [102,103]. It can be readily speculated that the ECMs derived from Schwann cells have direct effects to promote nerve repair after injury and exhibit great prospects in the construction of nerve scaffolds, which has been confirmed by several studies [104–106]. In addition, ECMs from many other somatic and stem cells, such as fibroblasts, various mesenchymal stem cells (MSCs) and pluripotent stem cells (PSCs), have also been shown to have excellent ability to promote nerve regeneration [107–109]. Similar to Schwann cell-derived ECMs, these ECMs are effective in promoting the adhesion, proliferation, and migration of Schwann cells as well as the extension of neurites, which offers the mechanistic basis for the applications of cd-ECMs for peripheral nerve tissue engineering. These contents are covered in detail in the subsequent application section.

Notably, ECMs derived from different cell sources show distinctive regulatory functions in tissue repair as well. Fibroblast-derived ECMs are noted to be enriched in pro-angiogenic proteins, and they can promote endothelial invasion and morphogenesis effectively. The hydrogel generated by fibroblast-derived ECMs can serve as a biomimetic substrate for vascularization. These suggest their future applications for inducing angiogenesis in tissue injury healing and regenerative contexts [110,111]. The fibroblast-derived ECM hydrogel is also demonstrated to be an excellent pro-regenerative biomaterial with immunomodulatory function, which can significantly alleviate pro-inflammatory cytokine and promote M2-type macrophages, along with significantly elevated vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) level [112]. Moreover, fibroblast-derived ECMs can be an amplification medium for MSC culture, which can facilitate the rapid proliferation of stem cells and maintain their stemness [113]. These functional properties may also be closely related to the neural repair capacity of fibroblast-derived ECMs. Stem cells have a unique capacity for self-renewal and multilineage differentiation as well as the potency to secrete various regulatory molecules, which contributes to forming a specialized niche and directing the development and regeneration of tissues [114]. ECMs derived from stem cells retain the specific functionality that can reflect *in vivo* microenvironment characteristics, and contain unique signaling networks to mediate cell behavior [115,116], which brings more opportunities to support peripheral nerve repair following injury. The ECMs derived from MSCs can effectively support stable cell expansion without heterogeneous reaction while maintaining the undifferentiated state of stem cells as well [117]. MSC-derived ECMs are demonstrated to prevent or reverse the senescence of stem cells, including neural progenitor cells (NPCs), bone marrow MSCs (BMSCs), and umbilical cord MSCs, thereby maintaining their ability to proliferate and differentiate. Various primary cells can also be refreshed by MSC-derived ECMs as well [74]. Moreover, MSC-derived ECMs can reduce the reactive oxygen species of MSCs and increase their antioxidant enzyme activity, thereby enhancing their oxidative resistance [118]. Not only that, in tissue repair, MSC-derived ECMs also exhibit immunomodulatory properties that restrain pro-inflammation and recruit more M2-type macrophages while achieving better vascularized

regeneration [119–122]. It is worth mentioning that the rejuvenation effect of MSC-derived ECMs primarily occurs thorough anti-oxidation and anti-inflammation [123,124]. Different from MSCs, PSCs have extensive lineage-specific differentiation potential into cells from all the three germ layers [125]. Therefore, the ECMs produced by the lineage-specific cells derived from PSCs, such as NPCs, are the focus of our attention. These ECMs retain the specific cues along tissue development, which can direct stem cell fate decisions. For example, the

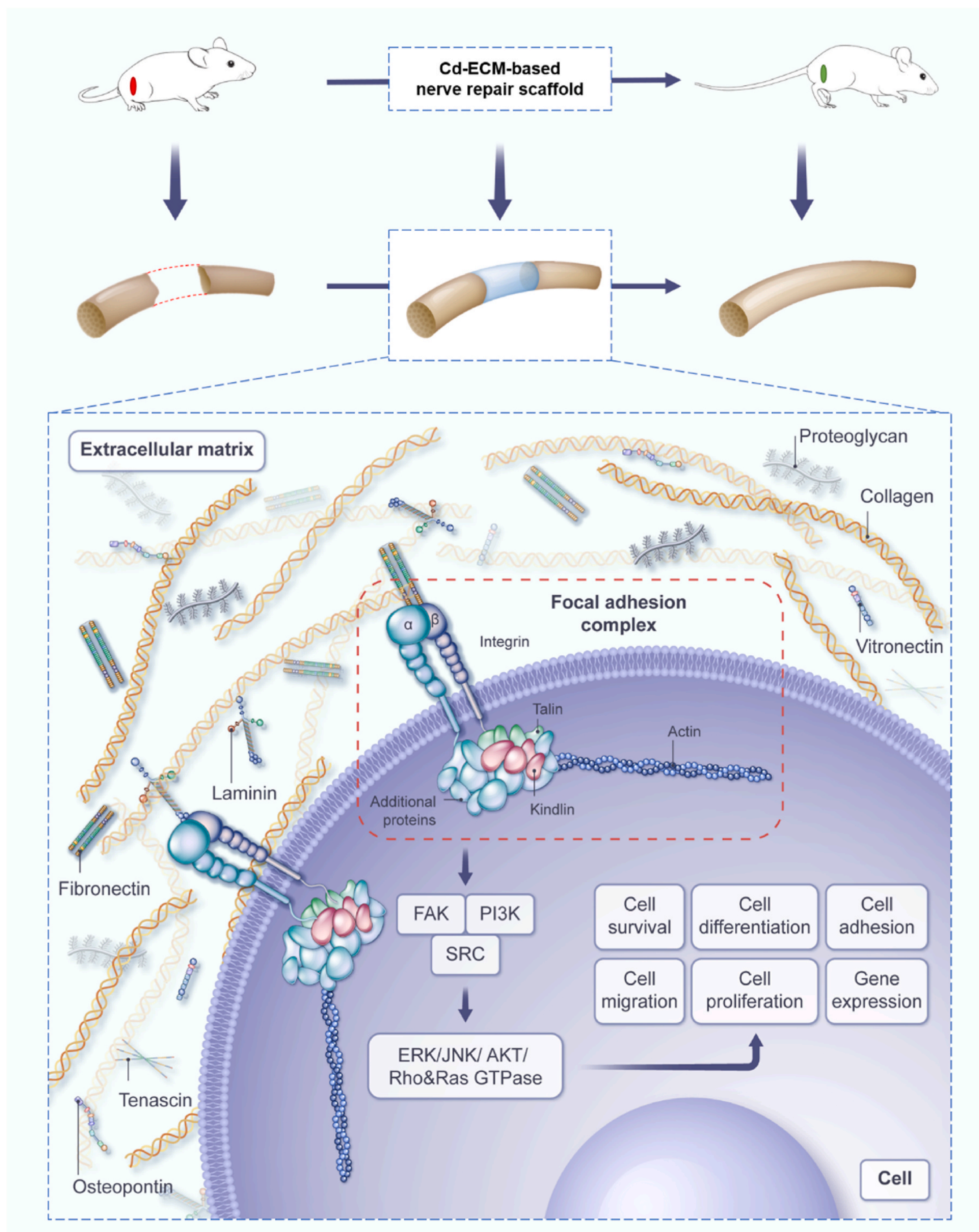

Fig. 2. Cd-ECM-based scaffolds regulate cell biological behavior through the interaction between bioactive components and integrins, thus promoting nerve regeneration. Following binding to the ligands in ECMs, the integrins cluster into focal adhesions, which leads to the assembly of numerous integrin-associated molecules in the focal adhesion complexes, thereby initiating a series of intracellular signaling cascades and causing the alteration of gene expression. The focal adhesion complexes mainly include cytoskeletal proteins, such as talin and kindlin, which link the complexes with actin cytoskeleton, as well as signaling and adapter molecules, such as FAK, SRC, and PI3K, which initiate canonical signaling pathways involving ERK, JNK, AKT, or small GTPases. ECM-integrin interaction plays an important role in the regulation of cell biological behavior, which provides the mechanistic basis for the applications of cd-ECMs for peripheral nerve tissue engineering.

ECMs from NPCs are enriched in various trophic factors such as brain-derived neurotrophic factor (BDNF) and FGF-2, which can guide neural-like differentiation and stimulate neurogenesis [126]. Stem cell-derived ECMs generally recapitulate the functions of their source cells. It is worth noting that stem cells themselves are proving to be an effective treatment for PNI [127]. Based on these functional mechanisms, the application potential of stem cell-derived ECMs as biomaterials in peripheral nerve tissue engineering is also worthy of expectation.

Cd-ECMs can establish an instructive regenerative niche for damaged nerves, which can provide structural support and modulate cell biological behavior through biochemical composition, sequestration of bioactive factors, and presentation of biomechanical cues [127,128]. Biochemical components allow cd-ECMs to anchor transmembrane receptors, such as integrins and other non-canonical receptors, to interact with cells [129]. These cell surface receptors connect the bioactive components of ECMs to the cytoskeleton and activate a series of intracellular signaling pathways, which plays a vital role in mediating cell adhesion, proliferation, migration, differentiation, and homing [130,131]. Moreover, cd-ECMs provide bind sites for various growth factors to modulate their bioavailability to achieve regulatory effects. Binding with ECMs can not only improve the stability of growth factors, but also enhance their functionality, which contributes to controlling their release and optimizing biological effects [132]. In addition, the mechanical environment established by cd-ECMs is a non-negligible element that affects cell behavior. Cells can sense physical properties of ECMs, including stiffness, porosity, topography, ultrastructure, and other biomechanical characteristics, and modify their shape, geometry, phenotype, function, and lineage commitment in response to the surrounding ECMs [129,133].

Cd-ECMs, as ECM-based biomaterials, exert their regulatory function mainly by interacting with integrins (Fig. 2). Integrins are the major cell-surface receptors linked between cells and ECM molecules [134–137]. There is substantial evidence to suggest that axon growth and extension are regulated in large part through ECM-integrin interaction that occurs during development and regeneration [138,139]. Integrins are transmembrane heterodimer receptors, composed of two non-covalent subunits α and β. The combination of dimers governs the specificity for their ligands, resulting in binding with different affinities to ECM molecules [85,140]. Once binding to the ligands in ECMs, integrins cluster into focal adhesions, leading to the assembly of numerous integrin-associated molecules in the focal adhesion complexes. The focal adhesion complexes consist mainly of cytoskeletal proteins, such as talin, kindlin, vinculin, and paxillin, which link the complexes with actin cytoskeleton, as well as signaling and adapter molecules, such as focal adhesion kinase (FAK), SRC Proto-Oncogene Non-Receptor Tyrosine Kinase (SRC), and integrin linked kinase, which initiate canonical signaling pathways involving ERK, JNK, AKT, or small GTPases [141–143]. The study of Gupton et al. revealed an integrin-dependent mechanism for neuritogenesis. The process occurs in the presence of laminin through integrin-dependent activation of FAK and SRC, and utilizes the regulating activity of the actin-related protein 2/3 complex and the exocytosis mediated by Vesicle Associated Membrane Protein 7 to coordinate actin cytoskeleton and membrane delivery, thereby driving axon development [144]. As with actin, the regulation of microtubule cytoskeleton is also critical for axon regrowth, and another study has demonstrated that directional microtubule assembly can also be modulated through the downstream of integrin signaling (FAK and synapses of amphids defective kinase), leading to axon initiation and growth [145,146]. Moreover, FAK and SRC have been shown to be associated with the formation of growth cone point contacts, the regulation of guidance cues as well as the turning of growth cones on laminin [147,148]. Notably, integrins also provide the physiological basis for mechanical transduction in nerve cells. In addition, mechanically sensitive ion channel proteins and G proteins are also important membrane proteins, which can transform ECM physical cues into intracellular biological signals to alter the behavior of nerve cells [149,150]. YAP/-TAZ has been recognized recently as a potent regulator for mechano-transduction signaling [151]. It is through these cellular regulatory mechanisms that cd-ECM-based scaffolds exert an important promoting role in the repair process of damaged peripheral nerves.

5. Preparation of cd-ECMs

The most widely used method of preparing cd-ECMs is monolayer cell sheet culture. Cell sheets are obtained by continuously culturing confluent cells *in vitro* without passaging [152]. It requires a long cell culture period of up to several weeks to harvest adequate amounts of cd-ECMs for the desired application. In addition to 2D monolayer culture system, 3D pellet culture system has been proposed to prepare cd-ECMs. This method involves centrifuging cells into pellets and then culturing them continuously to deposit ECMs. Cell aggregates have been used primarily to study the effects of cd-ECMs in regulating cell behavior [153]. Moreover, expanded cells can be seeded on 2D or 3D templates to establish tissue-engineered constructs depending on the application purpose [52]. This is the commonly used approach to fabricate nerve repair scaffolds using cd-ECMs at present (Fig. 3).

Supplementation of additional ascorbic acid is needed for robust cd-ECM generation and deposition. Ascorbic acid is a cofactor of lysyl hydroxylase and prolyl hydroxylase that are critical enzymes in collagen fibrillogenesis, and contributes to promoting cell sheet formation by increasing the amount of cd-ECMs [154,155]. Moreover, the addition of macromolecules, such as ficoll, carrageenan, polyvinylpyrrolidone, and dextran sulfate, to the culture system can also be effective in facilitating the formation of cd-ECMs [156,157]. These macromolecules can take up space to mimic crowded conditions of *in vivo* ECM deposition, which increases the effective concentration of bioactive molecules and the thermodynamic activity of the system [158,159]. Decreasing the serum concentration in the medium may help prevent the degradation of cd-ECMs caused by matrix metalloproteinases in serum, which provides favorable conditions for cd-ECM deposition [44]. It is worth noting that cell source is the primary determinant of the resulting cd-ECM composition. However, cells from different tissues possess different capacities to generate cd-ECMs. Further studies are necessary to determine the optimal culture conditions for various types of cells.

Once adequate cd-ECMs have been deposited, cellular components should be cleared up from ECMs through decellularization processing. Cellular components are the main source of allogeneic and xenogenic tissue immunogenicity, which may negatively influence or even terminate the regeneration process, possibly with graft rejection as a result [160,161]. Nevertheless, ECM molecules are highly conserved among species, and their immunogenicity is extremely low or even negligible [162]. The main aim of decellularization is to eliminate cellular antigens as much as possible, such as DNA, mitochondria, membrane lipids, and cytosolic proteins, in order to reduce the risk of adverse host immune response [163]. Meanwhile, the decellularization methods should be balanced against maintaining the molecular composition, biological activity, and structural integrity of the ECMs themselves. To date, several decellularization methods have been developed for cd-ECM production, including the combination of chemical, physical, and enzymatic methods (Fig. 3 and Table 2). Among them, the most basic strategy to prepare cd-ECMs is a treatment with the combination of mild chemical (Triton X-100/NH_4OH) and enzymatic reagents (DNase) [164]. Non-ionic detergent Triton X-100 can dissolve lipids on cell membranes, nuclear membranes, and organelle membranes by disrupting lipid-lipid and lipid-protein interactions, while leaving protein-protein interactions intact, which is described to cause minimal damage to native tissues [165,166]. The ECMs generated through Triton X-100 decellularization can preserve the capacity to bind and maintain the bioactivity of growth factors [127]. However, Triton X-100 may denature GAG content and affect collagen fiber structure [167]. Permeabilization of Triton X-100 allows NH_4OH to enter cells. NH_4OH not

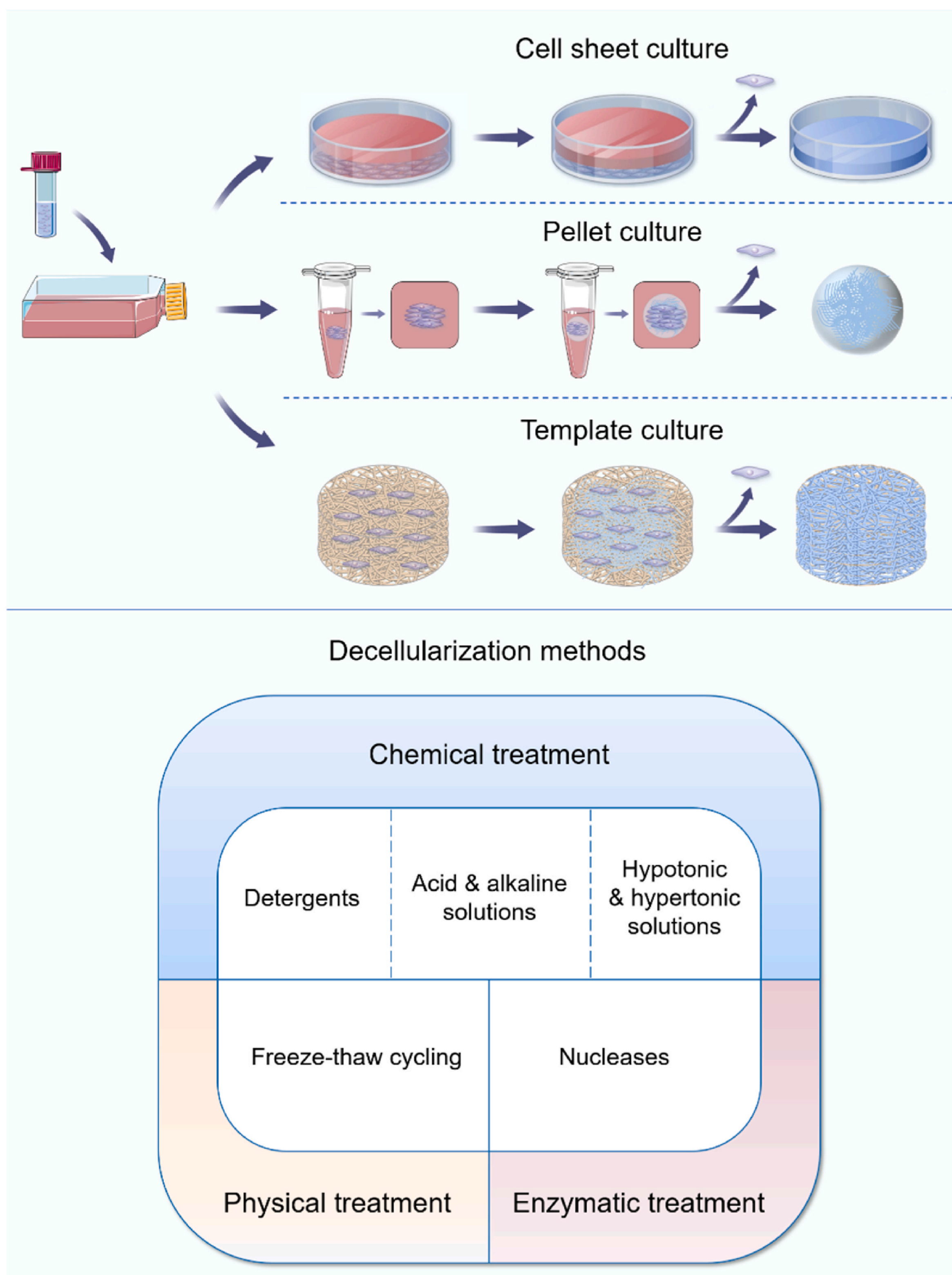

Fig. 3. Methods to prepare cd-ECMs. Depending on the application requirements, there are a variety of cd-ECM preparation methods to choose from. Source cells can be cultured continuously *in vitro* without passaging to form cell sheets. In addition, cells can also be centrifuged to form pellets and then deposit ECM. Cd-ECMs can also be deposited onto 2D or 3D templates to establish tissue-engineered constructs. Various forms of cd-ECMs are harvested after appropriate decellularization from cell sheets, cell aggregates, or templates. Physical, chemical, and biological decellularization methods can be used to prepare cd-ECMs, with the combination protocols of multiple methods being the most widely used.

Table 2
Decellularization methods for cd-ECMs.

Chemical/physical treatments	Enzymatic treatments	Reference
0.5 % Triton X-100 and 20 mM NH_4OH for 5 min	–	[107]
0.5 % Triton X-100 and 20 mM NH_4OH for 3 min	100 U/mL DNase for 3 min	[178]
0.5 % Triton X-100 and 20 mM NH_4OH at 37 °C for 5 min	100 U/mL DNase at 37 °C for 1 h.	[179]
0.5 % Triton X-100 and 20 mM NH_4OH at 37 °C for 5 min	100 U/mL DNase at 37 °C for 2 h.	[180]
0.5 % Triton X-100 and 20 mM NH_4OH at 37 °C for 10 min	200 μg/ml DNase and 200 μg/ml RNase at 37 °C for 1 h.	[181]
0.5 % Triton X-100 and 25 mM NH_4OH for 30 min	30 μg/mL DNase for 1 h.	[182]
1 % Triton X-100 and 20 mM NH_4OH for 5–10 min,	–	[106]
1 % Triton X-100 and 20 mM NH_4OH at 37 °C for 5 min	100 U/mL DNase for 3 min	[119]
3 % Triton X-100 and 2 % sodium dodecyl sulfate at 37 °C for 5 min	–	[183–185]
3 % Triton X-100 and 2 % sodium dodecyl sulfate at 37 °C for 5 min	100 U/mL DNase for 2 h	[186]
0.25 % Triton X-100 and 0.25 % sodium deoxycholate for 3–5 min	10 IU/mL DNase and 100 μg/ml RNase (gently wash)	[187]
3 % Triton X-100 and 10 % sodium deoxycholate at 37 °C for 15 min,	100 U/mL DNase for 2 h.	[104,105,108]
0.5 % Triton X-100 at 37 °C for 5 min and three freeze-thaw cycles (−80 °C/37 °C)	–	[166]
Four freeze-thaw cycles (−80 °C/room temperature) and 25 mM NH_4OH for 1 h	–	[173]
1 % Triton X-100 or containing 20 mM NH_4OH for 15–20 min	150 U/mL DNase at 37 °C for 30 min.	[188]
1 % Triton X-100 for 30 min,	2000 U/mL DNase for 30 min.	[109]
20 mM NH_4OH for 10 min	1000 U/mL DNase at 37 °C for 20–30 min.	[189]

only catalyzes the hydrolysis of the cytoplasmic components, but also leads to the destruction of nucleic acids [168]. The treatment with DNase and RNase can further remove nucleotides and elute cellular debris within tissues. These nucleases can cleave nucleic acid sequences by catalyzing the hydrolysis of the phosphodiester bonds in the ribonucleotide or deoxyribonucleotide chains, which results in the degradation of RNA or DNA, facilitating the removal of these molecules from ECMs [169]. In some studies, the ionic detergents sodium dodecyl sulfate and sodium deoxycholate were chosen to be used with Triton X-100 for the preparation of cd-ECMs. Both of them can solubilize the membranes of cell and nuclear. Sodium dodecyl sulfate tends to denature the proteins in ECMs and reduce the factor-binding affinity of ECMs. Sodium deoxycholate was reported to be more disruptive than sodium dodecyl sulfate, leading to the loss of ECM structure and components, especially GAGs, limiting the retention of growth factors [170–172]. In addition, freeze-thaw processing was also reported to be used to decellularize cell sheets [173,174]. Multiple freeze-thaw cycles can disrupt cell membranes through repeated formation of intracellular ice crystals, leading to cell lysis. In theory, freeze-thaw processing will only cause minor disruptions of ECM components and ultrastructure [175–177]. Notably, for cd-ECMs with minimal thickness and no intrinsic structure, the rate of temperature change should be carefully controlled to prevent ice formation from disrupting ECMs as well. However, although these decellularization methods are more commonly selected to generate cd-ECMs, their effectiveness on antigen removal and matrix retention has not been well validated. There is a need for improvement based on cell types, cell density, and ECM thickness to explore an optimal decellularization protocol for cd-ECMs.

6. Functional modification and enhancement of cd-ECMs

The applications of cd-ECMs as bioactive supplements have gradually been introduced into the field of regenerative medicine. However, the cd-ECMs generated by the traditional methods may not always achieve ideal restorative capacity for various tissues and organs, which makes it difficult to meet different clinical requirements. For cd-ECMs, the ease of *in vitro* modulation offers the opportunity to improve their bioactivity and functionality. The fine-tuning of culture conditions for source cells is a viable method to achieve biochemical ECM re-engineering. The direct supplementation of exogenous bioactive molecules, functional groups, and growth factors in culture medium can effectively remodel cd-ECMs for specific clinical applications [190,191]. Moreover, the extra addition of inducing compounds can also be used to impart the desired properties to ECMs. Cobalt can enhance the adaptive response of cells to hypoxia via activating hypoxia-inducible factor (HIF)-1, thus its chloride is often used in cell culture. Increased expression of HIF-1 was shown to promote the deposition of Collagen I, Collagen III, VEGF, and fibroblast growth factors in the ECMs generated, which would potentially result in a significant enhancement of tissue repair effects for cd-ECMs [192]. In addition, other changes in culture conditions, such as hypoxic cultures, can also influence the characteristics of ECMs by modifying the production of various bioactive components. Hypoxia was demonstrated to induce the generation of ECMs abundant in a variety of collagenous proteins and angiogenic factors, as observed in fibroblasts and MSCs [193,194].

It has to be mentioned that compared to the acellular matrices from tissues, cd-ECMs are characterized by insufficient mechanical properties and lack of internal microstructure, which greatly limits their direct applications in tissue regeneration following injury. Mechano-physical re-engineering of cd-ECMs is a necessary prerequisite for their clinical translation. Recently, the main strategy is to integrate cd-ECMs with synthetic biomaterials. Cd-ECMs can be used as scaffold coatings, imparting desired biological properties to the scaffolds [195]. In this method, source cells are seeded and cultured on the scaffolds followed by devitalization, leaving behind the ECMs secreted by cells that are deposited on the surface of the scaffolds. The prefabricated scaffolds offer mechanical and structural support, and the cd-ECMs on them offer biochemical cues. This is a commonly used method in the field of peripheral nerve repair [180,186]. Furthermore, physically mixing cd-ECMs with scaffold materials in advance is also a feasible method for the functional modification of scaffolds [52]. Homogenized ECMs are blended in the solution of scaffold materials in proper proportions, and then the solution is used to prepare composite scaffolds by manufacturing technologies. For example, ECM can be fabricated into nanofibers by electrospinning technology, which can generate fibrous and porous matrices with great cellular response controlling ability by varying fiber and pore sizes or fiber alignment. Studies on electrospun nerve scaffolds have focused on utilizing ECM to blend with other synthetic or natural polymers to assign specific bioactivity towards the electrospun fibers [196,197].

Not only that, crosslinking postprocessing could further optimize the mechanical properties of cd-ECMs, and even change their overall biological performance [198]. ECMs contain a variety of proteins with free amine or carboxyl groups, so they can be crosslinked on the polypeptide chains [199]. ECM-based biomaterials can resort to chemical crosslinking agents that endow the final construct with improved mechanical strength and enhanced resistance to enzymatic degradation after *in vivo* implantation. Chemical crosslinking is widely used for ECM postprocessing. The chemical agents can form covalent bonds between amino or carboxyl groups of different polypeptide chains in ECMs. Glutaraldehyde is a commonly used chemical crosslinking agent. It can establish a tightly crosslinked network by forming intermolecular bonds between amino groups [200,201]. Moreover, glutaraldehyde has superior efficiency in crosslinking distant protein molecules due to its self-polymerizing capacity. The ECMs crosslinked with glutaraldehyde

exhibit significantly enhanced physical stability [202,203]. However, glutaraldehyde has been shown to induce cytotoxic effects, which greatly limits its application [204]. Another chemical cross-linking agent, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), is used as an alternative to glutaraldehyde due to its good biocompatibility [205,206]. EDC mainly activates carboxyl groups, which react with free amino groups to form amide bonds. EDC is very efficient in crosslinking ECMs and optimizing their mechanical properties [207]. However, the physical stability of EDC-crosslinked biomaterials is weaker than that of glutaraldehyde-crosslinked biomaterials due to the weak capacity of EDC for crosslinking distal protein molecules [197]. Considering that ECMs are the biomaterials from tissues or cells, biological crosslinking strategies have received extensive attention. As a natural compound derived from gardenia fruits, genipin has shown to be a promising biological agent to crosslink ECM-based materials [208]. Genipin can bind with free amine groups of lysine or hydroxylysine. Because of its natural origin, genipin is proven to exhibit improved biocompatibility [209,210]. Genipin crosslinking can significantly improve physical properties of ECMs including tensile strength and resistance to enzyme degradation, even be more effective than EDC. Genipin crosslinking has been demonstrated to enhance the ECM bio-stability without affecting mesenchymal stem cell proliferation, and neural stem cell growth and differentiation [109,211]. Therefore, ECM-based biomaterials cross-linked with genipin are suggested to have great potential as scaffolds for nerve tissue applications.

Optimization of biochemical and mechano-physical properties of cd-ECMs allows for the regulation of gene expression and biological behavior of regenerative cells, which confers adequate capacity on ECMs to exert important roles in the repair process after nerve injury (Fig. 4).

7. Scalability of cd-ECMs

The scalability of cd-ECMs is a critical factor for their widespread adoption in biomedical applications. The transition from laboratory-scale production to industrial manufacturing requires innovative strategies to enhance efficiency and throughput. One of the major challenges in scaling up cd-ECM production is the expansion of cell cultures to provide sufficient biomass while maintaining the quality of ECMs. Traditionally, cell cultures have been performed in flasks and plates, which are labor-intensive and costly, especially when considering the high throughput required for industrial-scale cd-ECM production. To overcome these limitations, various cell culture platforms that can be adopted have been explored, including hollow fiber bioreactors, microcarriers, rocker bioreactors, and roller bioreactors, each offering unique advantages in terms of surface area to volume ratios, nutrient supply, and waste removal (Fig. 5) [212,213]. Hollow fiber bioreactors are particularly noteworthy for their cylindrical compartments packed with porous fibers that allow for nutrient exchange and waste removal, simulating the capillary structure of blood vessels. The large surface area of this system allows high cell densities to be achieved, making them a

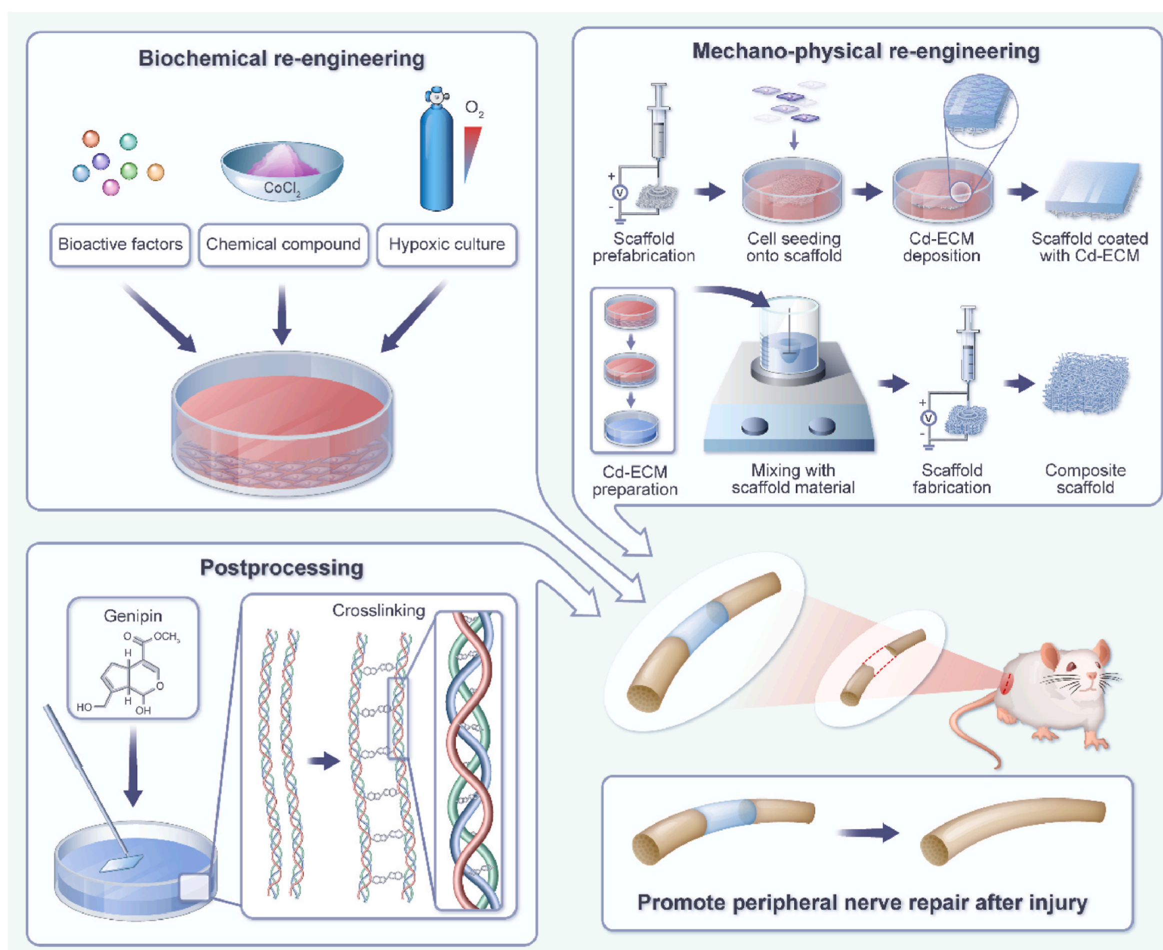

Fig. 4. The functional modification and enhancement of cd-ECMs. Multidimensional reengineering is a necessary prerequisite for the applications of cd-ECMs in nerve repair. Biochemical re-engineering of ECMs can be achieved by adding bioactive factors and chemical compounds or introducing hypoxic culture environment in the process of cell culture, which can render the desired functional properties of ECMs. Cd-ECMs can be used to coat prefabricated scaffolds, or to prepare composite scaffolds after dissolution for mechano-physical re-engineering. Moreover, postprocessing, such as cross-linking, can also improve the rigidity of cd-ECMs and optimize their overall biological performance.

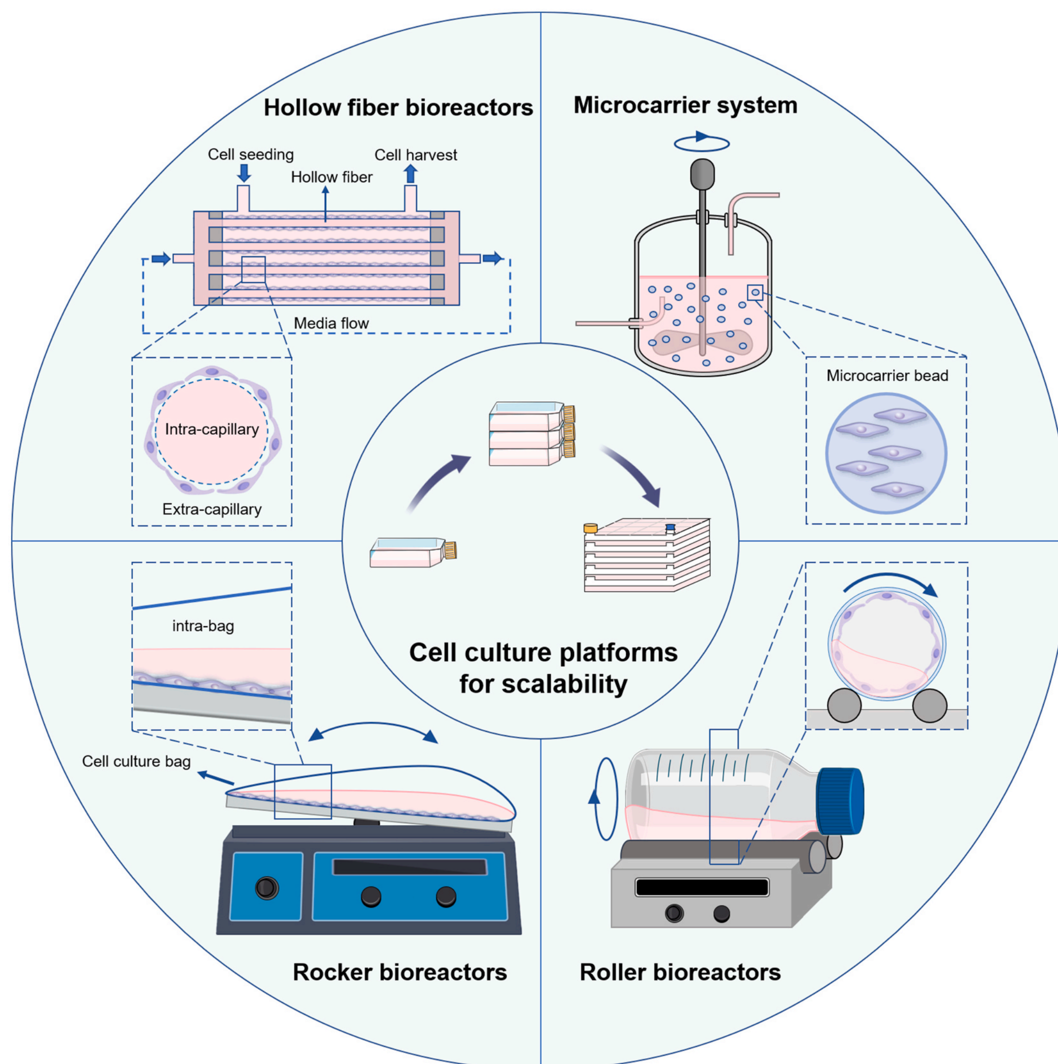

Fig. 5. Cell culture platforms for scalability. Hollow fiber bioreactors consist of cylindrical compartments equipped with porous hollow fibers, and the culture medium can flow through the fibers or the entire compartment or both. Cells can be seeded and cultured externally on the surface of the fibers, or cells can also be cultured internally. In microcarrier systems, cells can be cultured on the outer surface of the microcarriers, or they can migrate and attach inside the microcarriers depending on the type of microcarriers. The microcarriers are often used in conjunction with stirred tank bioreactors. The microcarriers are suspended in culture medium and moved around by the stirring motion. Rocker bioreactors can offer a gentle motion to culture medium by the periodic movement of the rocking platform, facilitating mass exchange between cells and medium. The roller bioreactors consist of cylindrical bottles placed on roller racks. These bottles are rotated in cylindrical motion. During the culture process, cells are submerged in the culture medium or exposed to gas inside the roller bottles.

promising option for cd-ECM production [214,215]. Microcarrier systems are another scalable solution, providing an expanded surface for cell attachment and growth compared to traditional 2D platforms. They can be customized with specific coatings to support various cell types [216]. Moreover, they are also extensively used in conjunction with stirred tank bioreactors, which facilitate nutrient distribution, further enhancing cell growth and ECM production. Rocker bioreactors can offer a gentle motion to culture medium by the periodic movement of the rocking platform, facilitating mass exchange between cells and medium and making them easily scalable and automatable. They have been successfully used for large-scale cell culture applications, demonstrating their potential for cd-ECM production [217,218]. Similarly, roller bioreactors, which involve the rotation of cylindrical bottles, are well-suited for adherent cells and can be scaled up by increasing the number of bottles used, although this can present challenges in terms of operational complexity due to the limited size of each bottle [219,220].

In addition, the development of stable and sustainable cell sources for ECM production remains an important issue worthy of investigation until now. Cell sources play a crucial role in ensuring the consistency of cd-ECM components. However, cells in continuous culture may show variability as the number of passages increases, especially stem cells, which may undergo senescence and loss of characteristics [221,222]. Theoretically, various primary stem cells possess the ability to perform adequate cell division for the large-scale production of ECMs. MSCs can have up to 13 to 25 population doublings before senescence [223]. Embryonic stem cells (ESCs) are usually considered immortal in culture [224]. Induced pluripotent stem cells (IPSCs) exhibit a normal karyotype during prolonged passaging without obvious senescence and loss of potency, so they also have the potential to be consistent sources of cd-ECMs [225]. Moreover, cell lines may be a much better alternative due to their capability of being maintained for a very long period. However, they may still lose their specific properties and require regular quality control [51]. Thus, more studies are necessary to verify the reliability and reproducibility of these source cells. It is worth noting that the yield of ECMs from various source cells can be optimized through small-molecule interventions or genetic engineering. Pharmaceutically active small molecules that target specific pathways involved in ECM deposition can be identified through high-throughput screening

and databases. These molecules can enhance the expression of the desired ECM components, thereby scaling up the production of cd-ECMs. It is crucial to carefully select and test these compounds and their working concentrations to ensure they do not adversely affect the cells or the final cd-ECM product, such as small molecule residues or off-target effects. Genetic engineering presents another avenue for enhancing cd-ECM yield. By stably overexpressing specific ECM proteins or modifying key pathways, cell lines can be developed to produce higher quantity and consistency of ECM components [226]. The use of gene-editing technologies like CRISPR allows for precise manipulation of the cell genome, enabling the creation of cell lines that are optimized for cd-ECM production [227]. This approach, however, requires careful consideration of cell types, desired ECM compositions, targeted functionality, and the cost of genetic manipulation. Compared to small-molecule interventions, genetic engineering to induce specific proteins is a more straightforward approach for the scalability of cd-ECMs.

8. Applications of cd-ECMs in peripheral nerve tissue engineering

Peripheral nerve repair after injury is still one of the most

Table 3
Applications of cell-derived ECMs for peripheral nerve tissue engineering.

Type of cd-ECMs	Study model	Basic scaffold	Effects	Reference
Schwann cell-derived ECM	*in vitro*	–	Promote axonal outgrowth of DRG neurons.	[104]
	in vivo (rat sciatic nerve gap)	Chitosan/silk fibroin scaffold	Regenerative outcomes achieved by cd-ECM-modified scaffolds were comparable to those of acellular nerve grafts, and superior to those of plain chitosan/SF scaffolds.	
Schwann cell-like cell-derived ECM (skin-derived precursor)	*in vivo* (rat sciatic nerve gap)	Chitosan/silk fibroin scaffold	Regenerative outcomes achieved by cd-ECM-modified scaffolds were comparable to those of acellular nerve grafts, and superior to those of plain chitosan/SF scaffolds.	[105]
Schwann cell-like cell-derived ECM (bone marrow mesenchymal stem cell)	*in vitro*	–	Promote axonal outgrowth of DRG neurons, but is less effective than Schwann cell-derived ECM.	[106]
	in vivo (rat sciatic nerve gap)	Poly (ε-caprolactone) conduit	Promote the repair of injured nerves and the restoration of gastrocnemius muscles, but the muscle recovery was inferior to that of Schwann cell-derived ECM.	
3T3 cell-derived ECM	*in vitro*	–	Promote neurite outgrowth from neurons in the superior cervical ganglia and maintain linear neurite directionality compared to fibronectin substrate.	[230]
L929 cell-derived ECM	*in vitro*	Polypyrrole-poly (lactide acid) fiber film	Promote cell adhesion, neurite outgrowth, and extension of PC12 cells.	[107]
Embryonic stem cell-derived neural progenitor cell-derived ECM	*in vitro*	–	Promote neural differentiation of the mouse embryonic stem cells and human induced pluripotent stem cells compared to the ECMs from undifferentiated ESC aggregates and spontaneously differentiated embryoid bodies.	[231]
Embryonic stem cell-derived neural progenitor cell-derived ECM	*in vitro*	–	Promote neural differentiation of dental follicle mesenchymal stem cells.	[232]
Induced pluripotent stem cell-derived neural progenitor cell-derived ECM	*in vitro*	–	Support induced pluripotent stem cells expansion and maintenance of their pluripotency as well as enhance neural differentiation.	[178]
Pluripotent stem cell-derived ECM	*in vitro*	–	Modulate the proliferation and differentiation of neural progenitor cells.	[109]
Umbilical cord mesenchymal stem cell-derived ECM	*in vitro*	–	Promote the proliferation of Schwann cells and the axonal outgrowth of DRG neurons. Upregulate gene and protein expression levels of growth factors in Schwann cells.	[179]
Umbilical cord mesenchymal stem cell-derived ECM	*in vitro*	Polycaprolactone/silk fibroin material	Bring sufficient bind sites for Schwann cells, and provide superior support for their proliferation and extension, as well as subsequent axon regrowth and angiogenesis.	[180]
	in vivo (rat sciatic nerve gap)	Polycaprolactone/silk fibroin scaffold	Cd-ECM-modified scaffolds accelerated early regeneration efficiency and improved the final repair effect of sciatic nerve defects, achieving superior muscle and functional recovery, which reached the level of autologous nerve grafts.	
Bone marrow mesenchymal stem cell-derived ECM	*in vivo* (rat sciatic nerve gap)	Chitosan/silk fibroin scaffold	Regenerative outcomes achieved by cd-ECM-modified scaffolds were superior to those of plain chitosan/SF scaffolds.	[183]
Bone marrow mesenchymal stem cell-derived ECM	*in vivo* (rat sciatic nerve gap)	Chitin/chitosan fibers scaffold	Cd-ECM-modified scaffolds exhibited good supporting capacity for axon regrowth and myelin formation, which can effectively restore nerve conduction function, achieving excellent sensory and motor recovery, similar to autologous nerve grafts.	[186]
Bone marrow mesenchymal stem cell-derived ECM	*in vitro*	Chitosan/silk fibroin scaffold	Promote the proliferation of Schwann cells and the axonal outgrowth of DRG neurons.	[184]
	in vivo (dog sciatic nerve gap)	Chitosan/silk fibroin scaffold	Regenerative outcomes achieved by cd-ECM-modified scaffolds were comparable to those of autologous nerve grafts.	
Bone marrow mesenchymal stem cell-derived ECM	*in vitro*	–	Promote axonal outgrowth of DRG neurons, and is significantly more effective than the ECMs derived from Schwann cells, skin-derived precursor Schwann cells, and fibroblasts.	[108]
	in vivo (rat sciatic nerve gap)	Chitosan/silk fibroin scaffold	Cd-ECM-modified scaffolds can better mediate the effective recovery of axonal transport and conduction while enhancing axonal regrowth and remyelination, leading to superior muscle and function restoration compared with the other ECMs.	
Bone marrow mesenchymal stem cell-derived ECM	*in vivo* (rat sciatic nerve gap)	Chitosan/PLGA fibrous scaffold	Cd-ECM-modified scaffolds exhibit sustained high levels of regulation in axon and myelin regeneration and play a significant role in regulating ECM mediation, vascularization, and immune response over time. They achieve comparable effects on nerve repair and functional recovery as autografts.	[185]

challenging tasks and concerns in neurosurgery [228]. ECMs are pivotal in establishing an ideal microenvironment for peripheral nerve regeneration, and ECM-based grafts are considered promising alternatives to autologous nerve grafts [229]. Given the robust activities of cd-ECMs in regulating cell behavior and their advantages over td-ECMs, the applications of cd-ECMs in peripheral nerve tissue engineering have been widely investigated (Table 3).

8.1. Schwann cell-derived ECM

In the peripheral nerve system, Schwann cells, as the major glial cells, play a key role in the formation and organization of neural ECMs, in particular the basal lamina that is considered an ECM layer, mainly composed of collagen, laminin, and fibronectin [233,234]. Therefore, the neurorestorative effects of ECMs derived from Schwann cells have received great attention. In the study of Gu et al. [104], Schwann cells were cultured on the chitosan conduits filled with silk fibroin (SF) fibers to deposit ECMs for modification. They found that Schwann cell-derived ECMs significantly facilitated axon outgrowth from dorsal root ganglion (DRG) neurons *in vitro*. Moreover, the *in vivo* results demonstrated that the Schwann cell-derived ECM-modified chitosan/SF scaffolds exhibited superior repair capacity than the plain chitosan/SF scaffolds. Notably, the regenerative outcomes achieved by the modified scaffolds were comparable to those of acellular nerve grafts, indicating that despite the discrepancies in composition and structure between Schwann cell-derived ECMs and nerve tissue-derived ECMs, their neurotrophic and neuroprotective functions were similar to each other.

8.2. Schwann cell-like cell-derived ECM

The applications of Schwann cells as the matrix source are greatly restricted by the inherent drawbacks, such as limited cell sources, long duration of *in vitro* culture, slow proliferation rate, and difficulty in purification [235]. Therefore, the development of alternatives to Schwann cells has been extensively explored. Skin-derived precursors, similar to Schwann cells, are also a type of cells derived from the neural crest. These cells are easily harvested from adult skin tissue of both rodents and humans, and they can differentiate into Schwann cell-like cells when exposed to the appropriate growth factors. In another study by the research group of Gu et al. [105], skin-derived precursors were extracted and pre-differentiated into Schwann cell-like cells. The ECMs derived from these Schwann cell-like cells were used to optimize chitosan/SF scaffolds. The results obtained in this study are close to their previous studies [104]. The ECM-modified chitosan/SF scaffolds exhibited significantly enhanced neurorestorative effects, which reached the extent of acellular nerve grafts composed of nerve tissue-derived ECMs. Moreover, BMSCs are readily available through routine protocols and can be expanded in bulk by *in vitro* culture. Due to their neural differentiation potential, BMSCs are also extensively selected as an important source of Schwann cell-like cells. In the study of Zhao et al. [106], Schwann cell-like cells transdifferentiated from BMSCs were introduced as parent cells to generate matrices for constructing ECM-modified nerve scaffolds. They observed that the axon growth of DRG neurons cultured on both the cd-ECMs of Schwann cell-like cells and Schwann cells was significantly enhanced, but the former was inferior to the latter. In addition, under *in vivo* conditions, these two cd-ECMs were able to promote the repair of injured sciatic nerves. However, Schwann cell-like cell-derived ECMs are less effective than Schwann cell-derived ECMs in the recovery of gastrocnemius muscles, suggesting a significant difference in molecular compositions between the two cd-ECMs.

8.3. Fibroblast-derived ECM

Fibroblasts are also the predominant cell types found in the peripheral nervous system. Following PNI, fibroblasts, like Schwann cells, are responsible for generating new ECMs to direct cell migration and axon regeneration [236]. Considering the ECMs secreted by fibroblasts are abundant in collagen, laminin, and fibronectin similar to Schwann cell-derived ECMs [237], these non-nerve cell-derived ECMs have also been attempted to optimize the biomaterials for nerve tissue engineering. The study of Harris et al. demonstrated that the ECMs derived from 3T3 cells were more effective in promoting neurite outgrowth from neurons in the superior cervical ganglia than fibronectin substrate. The neurites on the cd-ECMs were not only able to extend robustly, but these radially projecting neurites were organized in largely parallel arrays, which is drastically different from the neurites cultured on the fibronectin substrates alone that develop along circuitous routes frequently crossing over other neurites, suggesting that 3T3 cell-derived ECMs were conducive to the maintenance of linear neurites directionality [230]. In the study of Zhou et al. [107], PC12 cells cultured on the polypyrrole-poly (lactide acid) fiber-film coated with L929 cell-derived ECMs exhibited significant increases in cell adhesion rate and neurite-bearing cell rate. Meanwhile, the neurite extension and alignment along the fiber axis were also significantly enhanced. These further confirm the application potential of fibroblast-derived ECMs in PNI treatments.

8.4. Pluripotent stem cell-derived ECM

PSCs, including ESCs and iPSCs, have the ability to proliferate indefinitely, and are therefore considered to be unlimited sources of cd-ECMs [238,239]. Compared to somatic cd-ECMs, PSC-derived ECMs are characterized by the scalability for ECM generation as well as the unique capacity to direct stem cell fate decision and recapitulate tissue morphogenesis niche [240]. PSCs were found to secrete a large amount of endogenous ECM components, including fibronectin, laminin, Collagen IV, vitronectin, and GAGs, which are involved in several signaling pathways that affect tissue development [241]. It is worth noting that the secretory profiles of PSC-derived ECMs can be influenced by lineage specifications. The PSC-derived ECMs exhibit distinct compositions and signaling capacities that reflect the characteristics of their developmental stages [242]. The directed differentiation of PSCs can regulate the properties of ECMs, which may induce the commitment of reseeded undifferentiated cells towards the phenotype of the source cells that generate cd-ECMs [243,244]. Yan et al. demonstrated that the ECMs derived from ESC-derived NPC (ESC-NPC) aggregates were more competent in promoting neural differentiation of the mouse ESCs and human iPSCs compared to the ECMs from undifferentiated ESC aggregates (EAs) and spontaneously differentiated embryoid bodies (EBs). The proteomic analysis revealed that ESC-NPC-derived ECMs were significantly different from those of the other two groups. The ECMs expressed higher levels of matrix proteins that promote neural tissue development, including laminin-related peptides, heparin sulfate proteoglycan core protein, and Collagen IV. Moreover, ESC-NPC-derived ECMs retain several neurotrophic and neuroprotective molecules, such as neuron-derived neurotrophic factor, activity-dependent neuroprotective protein, and hepatoma-derived growth factor. These results explain the distinct cellular response to the ECMs derived from ESC-NPCs compared to EAs and EBs [231]. Not only that, in the study of Heng et al. [232], ESC-NPC-derived ECMs have been shown to enhance the neurogenic potential of dental follicle MSCs, which provides suitable templates to regulate stem cell fate decision. Besides ESC-NPC-derived ECMs, the ECMs produced by NPCs derived from iPSCs also exhibit the potential to recreate the neural niche. The iPSCs cultured on iPSC-NPC-derived ECMs can be directed for neural differentiation as well [178]. In addition, Sart et al. demonstrated that the cross-linked scaffolds composed of the ECMs generated by PSCs at different developmental stages can regulate neural differentiation of the reseeded cells through the tunable biophysical and biological properties, further confirming the great application potential of PSC-derived ECMs [109]. However, prior to clinical translation, it is essential to evaluate the functionality of PSC-derived ECMs in repairing peripheral nerve defects

by *in vivo* transplantation experiments.

8.5. Mesenchymal stem cell-derived ECM

MSCs are adult stem cells derived from connective tissues, and are recognized as a promising cell source for tissue engineering. Similar to PSCs, MSCs are capable of producing a significant amount of endogenous ECMs, reflecting their *in vivo* microenvironment [245–247]. The ECMs derived from MSCs mainly contain Collagen I, Collagen IV, vitronectin, laminin, decorin, biglycan, and perlecan [248]. Moreover, MSCs were shown to secrete various growth factors, such as insulin-like growth factor I, transforming growth factor-β, FGF-2, VEGF, and platelet-derived growth factor, which can interact with ECMs and participate in the paracrine and autocrine signaling that regulates cell proliferation and differentiation [249,250]. These bioactive ECM components and growth factors secreted from MSCs form an instructive niche for self-renewal and lineage commitment. There has been extensive research on the applications of MSC-derived ECMs in peripheral nerve tissue engineering due to their potent bioactivities. The study of Xiao et al. demonstrated that umbilical cord MSC-derived ECMs were competent to provide a beneficial niche for nerve regeneration. They can not only enhance the proliferation of Schwann cells and the neurite growth of DRGs, but also upregulate gene and protein expression levels of BDNF, glial cell-derived neurotrophic factor, and VEGF in Schwann cells [179]. Moreover, Guan et al. further confirmed that umbilical cord MSC-derived ECMs can offer adequate anchorage for Schwann cells and subsequent axon regrowth and angiogenesis, thereby supporting the rapid progression of these important regenerative processes. Their *in vivo* results showed that the polycaprolactone/silk fibroin (PCL/SF) conduits modified with cd-ECMs obtained a significant increase in nerve repair capacity and reached a level similar to autologous nerves. The modified conduits achieved highly remarkable restoration of nerve conduction, as well as muscle and functional recovery [180].

BMSC-derived ECMs were also confirmed to possess superior biological properties in peripheral nerve repair. The studies of Gu et al. and Qi et al. have shown that BMSC-derived ECMs can not only directly promote the regeneration of injured nerves, but that their addition can also significantly improve the repair capacity of nerve scaffolds. Compared with the plain scaffolds, the BMSC-derived ECM-modified scaffolds can guide more nerve fibers across the defects and re-enter the distal nerve segments, allowing for superior restoration of innervated muscles and motor function [183,186]. The unique neural activity of BMSC-derived ECMs was further clarified by the study of Xue et al. [184]. Their *in vitro* findings demonstrated that BMSC-derived ECMs could effectively enhance the ability of nerve scaffolds to support axon extension and Schwann cell proliferation. Unlike other studies using the rat sciatic nerve defect model, the nerve scaffolds modified by BMSC-derived ECMs were utilized to bridge 60-mm sciatic nerve gaps of dogs in this study. The modified scaffolds were shown to possess markedly promoting effects on peripheral nerve regeneration, achieving satisfactory restorative results comparable to those of autologous nerve grafts.

The study of Wang et al. compared the protein components and spatial organizations of the ECMs secreted by BMSCs, Schwann cells, skin-derived precursor Schwann cells, fibroblasts, and acellular nerves, and assessed their effects on nerve repair comprehensively [108]. BMSC-derived ECMs were confirmed to share more similar proteomic and microstructural characteristics with acellular nerves than the other ECMs, indicating that BMSC-derived ECMs have the potential to better reproduce the tissue-specific biochemical and biophysical cues of native neural ECMs. The *in vitro* and *in vivo* results further revealed that BMSC-derived ECMs can better mediate the effective recovery of axon transport and conduction while enhancing axon regrowth and remyelination, leading to superior muscle and function restoration compared with the other ECMs. In addition, the regenerative microenvironment formed by BMSC-derived ECMs was demonstrated to be characterized by increased expression of factors related to nerve repair and reduced immune response, which more closely resembles that of autologous nerve grafts, suggesting that BMSC-derived ECMs can construct more superior microenvironment for peripheral nerve regeneration than the other ECMs.

In a recent study by Wang et al. [185], unlike other previous studies using cd-ECMs as coating materials, they devised a novel method to construct nerve grafts. The gelatinous membrane-like BMSC-derived ECMs with PLGA fibrous scaffolds as the axis were rolled into 6 to 8 layers and encapsulated into chitosan conduits to develop three-dimensional matrix-based oriented nerve grafts. This study further analyzed the nerve repair efficacy and functional mechanisms of BMSC-derived ECMs by comparing the novel nerve scaffolds modified by ECMs with autologous nerve grafts to bridge the sciatic nerve defects of rats. The results confirmed the excellent ability of BMSC-derived ECMs to construct neuroregenerative microenvironments. The grafts modified by BMSC-derived ECMs achieve comparable effects on nerve repair and functional recovery as autografts. However, the BMSC-derived ECM group exhibits more complex molecular regulations. Although the regulations of ECM and vascularization are similar with substantial molecular regulatory changes at the beginning of ECM modified scaffolds and autografts, the ECM modified scaffolds exhibit sufficient capacity for sustained high levels of regulation in axon and myelin regeneration. Not only that, immunomodulation in the ECM group peaked at 2 weeks postoperatively and then returned to normal levels, which contrasted markedly with the absence of significant activation of autografts. These findings demonstrated that the exceptional biochemical and structural components in BMSC-derived ECMs play an important role in promoting initial cell adhesion and guidance, as well as exerting spatio-temporal control over the microenvironment to stimulate continuous cellular responses that facilitate peripheral nerve regeneration.

9. Conclusion and outlook

The applications of cd-ECMs in peripheral nerve tissue engineering have received widespread attention, and research in this area has been continuously explored in the last decade. Cd-ECMs avoid the safety issues associated with ts-ECMs, and have many advantages, including the feasibility of *in vitro* preparation, accessibility of autologous cell sources, and tunability of ECM properties. Current studies have confirmed that cd-ECMs have an excellent capacity to promote nerve regeneration following PNI, exhibiting significant clinical potential.

Although considerable progress has been made in the development of cd-ECM-based nerve grafts, there are several challenges that remain to be further addressed. Firstly, research on the mechanism of cd-ECMs promoting nerve regeneration should be more comprehensive. With the continuous deepening of research, studies on the applications of cd-ECMs in nerve tissue engineering have evolved from the development of ECM-based scaffolds and the assessment of repair capacity to the exploration of underlying mechanisms. Recent studies have analyzed the compositional profiles of cd-ECMs and investigated their mechanistic roles through proteomics, RNA-seq, and bioinformatics technologies. However, in addition to biochemical components, the physical performance of ECMs is also an important determinant of their cellular regulatory effects. Therefore, it is necessary to further analyze the neural repair mechanisms of cd-ECMs from the aspect of their mechanical and topographical properties. Secondly, in the preparation of cd-ECMs, universal decellularization methods, whether chemical, physical, or biological, may result in a significant loss of bioactive components in the matrix, affecting the pro-regenerative capacity of cd-ECMs. Therefore, it is necessary to devise a decellularization protocol specifically suitable for cd-ECMs. Distinguishing from the effect mechanism of conventional decellularization methods, decellularization by intentional activation of programmed cell death is an appealing proposal. By inducing cell death through the apoptotic pathway, dying cells fragment into small

apoptotic bodies, which could theoretically be more readily removed by rinsing with little damage to the ECMs. This is a meaningful optimization direction for cd-ECM decellularization technology, which deserves further study. Thirdly, to date, cd-ECMs used in the research of nerve repair have been derived from unmodified tissue-specific somatic cells or stem cells, which may be less ideal for achieving the preferable therapeutic outcome. It is necessary to seek strategies for customizing cd-ECMs to meet the functional properties required for peripheral nerve regeneration. In addition to genetic engineering mentioned above, the applications of the ECMs deposited by multiple cultured cells are a research direction worth exploring. Co-culture ECMs can gain further enhanced regulatory capacity, leading to a significant increase in tissue repair effects, which has been validated in other tissues. This can provide a more effective response to the complex microenvironment of nerve regeneration. The synergistic effects of the components in co-culture ECMs need to be clarified in future studies to modulate their functional specificity. It must be mentioned that the current modifications to cd-ECMs are mainly focused on biological manipulation. Cross research at the interface to other disciplines such as material science is essential to enable further development of cd-ECMs. Fourthly, in constructing engineered nerve grafts, cd-ECMs have been used almost exclusively as coating materials for surface modification of scaffolds at present. However, considering the versatility of ECMs, cd-ECMs are also available in various application forms like ts-ECMs, such as powders, hydrogels, and bio-inks. ECM powders can fill areas and mold with the shape of tissue defects. This capacity to conform is their advantage. In the treatment of nerve injury, ECM powders processed into sheets or incorporated into other gels to enhance substrate bioactivity may be feasible options. Cd-ECM powders can be further solubilized and manipulated to form hydrogels. ECM solutions can self-assemble into a hydrogel upon incubation at physiological temperature (37 °C) or *in vivo* implantation, which confers greater utility for cd-ECM hydrogels in the construction of nerve grafts. In addition, the application potential of cd-ECM hydrogels is increased by their compatibility with a variety of process technologies such as 3D bioprinting. Cd-ECM bio-inks have inherent advantages due to their preservation of native biochemical cues, which has received increasing attention. 3D bioprinting has the characteristics of assembling the spatial patterning of biological materials to construct tissue analogs through layer-by-layer deposition. Therefore, the applications of cd-ECMs as bio-inks with tailormade bioactivities for 3D bioprinting provide a feasible solution of nerve mimic spatial construction. All these material forms of cd-ECMs have excellent potential for application in peripheral nerve tissue engineering and deserve further investigation. Finally, the large-scale production of cd-ECMs remains a major challenge for their clinical translation. Although the scalability technologies of cd-ECMs have gained significant progress, some concerns are required to be considered. The culture parameters of the dynamic bioreactor platforms, such as perfusion rate, swing frequency, or rotation speed, may affect the components and proportion of the obtained cd-ECMs. Thus, it is essential to fully characterize the ECM products before adopting these culture technologies for mass production. Also, the manner in which cd-ECMs are harvested from these dynamic culture systems needs to be carefully designed. The subsequent process should circumvent influences on the composition of the output cd-ECMs while avoiding the introduction of unnecessary contamination. Moreover, there is no uniform manufacturing standard for cd-ECMs, which leads to difficulties in their quality control. The further exploration of sustainable and efficient biomanufacturing methods for cd-ECMs will be the focus of future research. There has been relatively little progress in the applications of cd-ECMs over the past few years, mainly due to scalability issues. Efforts should be made to address this challenge, which will bring great rewards.

In conclusion, cd-ECMs represent a highly promising strategy for peripheral nerve repair and possess great value for clinical application. Although there is still a long distance to transfer from the bench to the bedside, cd-ECMs are far from reaching their full potential. Innovative methodological advancements and broad interdisciplinary research are expected to pave the way for the further development of cd-ECMs in nerve tissue engineering.

CRediT authorship contribution statement

Yingxi Xu: Writing – original draft, Methodology, Investigation, Funding acquisition. **Xianbo Liu:** Writing – original draft, Visualization, Investigation. **Muhammad Arslan Ahmad:** Writing – review & editing, Validation. **Qiang Ao:** Supervision, Software, Resources. **Yang Yu:** Writing – review & editing, Project administration, Conceptualization. **Dan Shao:** Writing – review & editing, Conceptualization. **Tianhao Yu:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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