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The Potential of Decellularized Cell-Derived Matrices for Biomedical Applications

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Abstract—Decellularized extracellular matrices show a great promise as materials for tissue engineering and regenerative medicine. Recently, there has been an increasing interest in the use of cell-derived extracellular matrices (CD-ECMs). The present mini-review focuses on advantages and disadvantages of the CD-ECMs, describes the variety of approaches to modify the CD-ECMs and discusses the CD-ECMs application fields. In particular, CD-ECMs were shown to serve as cell culture substrate, as base for biocompatible scaffold production, as drug for cell-free therapy and as component of disease models.

Keywords: decellularized matrix, cell-free matrix, cell-free therapy, tissue engineering, regenerative medicine

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INTRODUCTION

A multicellular organism is organized into a single whole due to the extracellular matrix (ECM). ECM is a complex structure consisting of three-dimensional fibrillar protein network within the proteoglycan gel. Along with structural proteins, ECM contains so-called matricellular proteins regulating cell functions, and deposits growth factors and other signaling molecules. From a functional perspective, ECM is not just a cement connecting cells into tissues and organs. ECM provides a substrate for cell adhesion and migration, maintains the appropriate environment, deposits nutrients and signaling molecules controlling multiple cell functions such as proliferation, differentiation and even cell death. Besides, ECM determines organ shape and mechanical properties of tissues, plays key roles in development and regeneration, and maintains tissue homeostasis.

Obviously, ECM is the most natural substrate for the existence and functioning of cells. ECM is a point of interest for tissue engineering and regenerative medicine fields because of its unique biological activity and excellent biocompatibility. Usage of ECM in bioengineering studies (development of artificial tissues and organs, vascular prostheses *et cetera*) has become a true trend in recent decades. ECM-based products have been successfully used in clinics. To date, more than 80 approved ECM-based products are applied in orthopedics, dentistry, cardiovascular and plastic surgery (Parmaksiz et al., 2016). For instance, Alloderm product (acellular matrix of human skin) has proved its effectiveness in more than million application cases for treatment of burns, wounds, gum recession, mammoplasty *et cetera* (Konofaos et al., 2017). Restoration of walking function in patients with volumetric muscle loss with the use of decellularized pig bladder that served as scaffold for muscle regeneration (Sicari et al., 2014) is an encouraging achievement, demonstrating that usage of ECM opens up new horizons for medicine.

Decellularized (i.e. physically or chemically treated in order to remove cellular component) organs and tissues are traditional ECM sources. In recent years interest in cell-derived ECM (CD-ECM) has grown. In this mini-review we consider benefits and drawbacks of such ECM source and assess its prospects of using.

CD-ECM ADVANTAGES AND DISADVANTAGES

Advantages

Firstly, cell-derived extracellular matrices can be an alternative to ones of xenogeneic or allogeneic origin. Commercially available acellular products are extracted from animal or human tissues, and although highly conserved ECM components are considered to be non-immunogenic (Cheng et al., 2014), ECM-based xenografts and allografts harbour the risk of an immune response and rejection, likely because of incomplete cell removal or ECM proteins modification during decellularization (Methe, 2020; Massaro

Abbreviations: ECM, extracellular matrix; CD-ECM, cell-derived extracellular matrix; iPSC, induced pluripotent stem cells; MSCs, mesenchymal stromal/stem cells; ESC, embryonic stem cells.

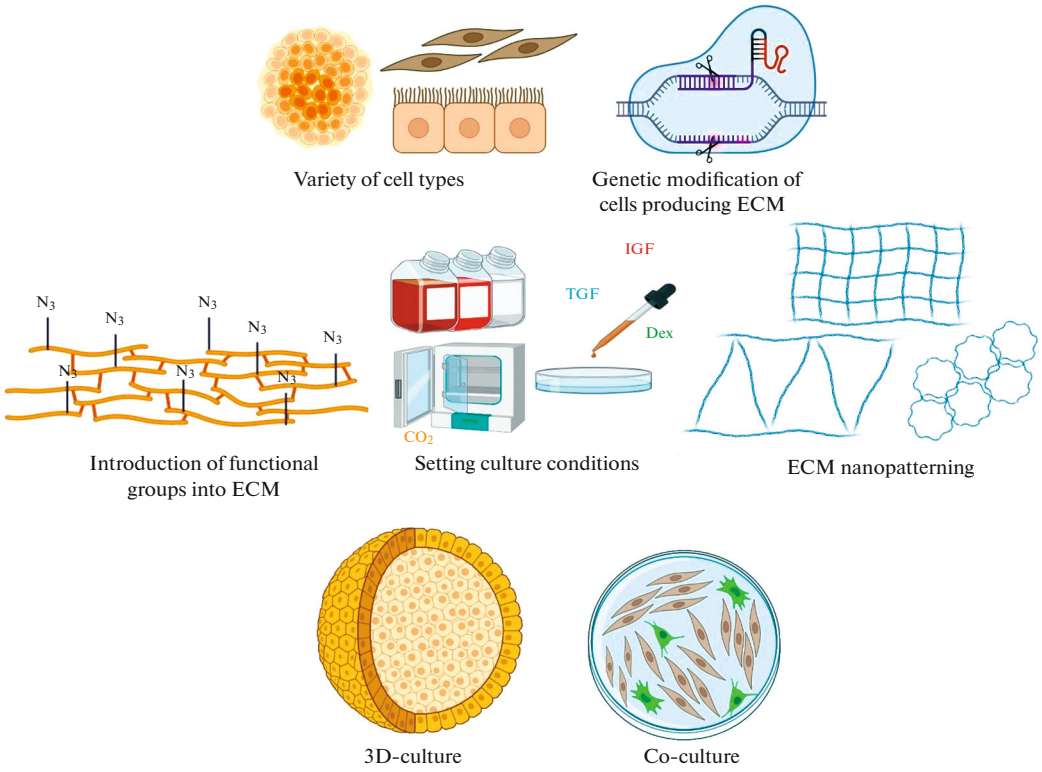

Fig. 1. CD-ECM customization potential. Created on BioRender.com

et al., 2021). Besides, usage of allogeneic (cadaveric) human tissues as ECM source are related to disease transmission risks as well as to ethical and logistic concerns. These difficulties can be overcome by using the recipient's own cells as ECM source. Similarly, CD-ECM based materials can serve as an alternative to autografts. Although autografts are considered the gold standard, for example, in bone surgery, autogenous bone graft is a limited resource with determined shape and size; in addition, complications can occur at donor site. Alternatively, an appropriate graft may be engineered with the use of patient mesenchymal stem/stromal cells or osteogenic cells producing bone matrix (Cheng et al., 2014).

Secondly, cell culture can produce ECMs that are difficult or impossible to isolate from tissues. For instance, dense cartilage matrix is low-permeable for decellularization agents (Zhu et al., 2021); stem cell niche can barely be extracted from tissues, but specific niche matrix environment can be imitated with use of MSC-produced ECM (Assunção et al., 2020). Relative simplicity of CD-ECM handling makes it possible to use milder decellularization methods: for example, CD-ECM can be obtained without use of detergents, thus ensuring absence of residuals that can cause adverse reactions and affect ECM structure (Nellinger et al., 2022).

Thirdly, CD-ECMs have considerable customization potential. Compared to organ- or tissue-derived ECMs whose structure and composition are determinate, ECMs secreted by cell cultures can be tailored for specific purposes (Fig. 1). All the variety of cell lines or primary cultures can be engaged in ECM in vitro production; cells can also be genetically modified (for example, for ECM components overexpression). Thus, human bladder carcinoma cell line 5637 transfected with vector carrying fibronectin gene was used for modification of PLA scaffold with ECM; modified scaffold was demonstrated to exert biological influence upon Hep2G hepatocytes, suggesting that it can be implicated in liver tissue engineering (Grant et al., 2018). Placenta-derived MSCs immortalized with hTERT transduction were shown to secrete biologically active ECM over many passages (Kusuma et al., 2017). Along with many other cell types, induced pluripotent stem cells (iPSC) are also of interest; it was shown that iPSC-derived fibroblasts demonstrate augmented ECM proteins production compared to cells before reprogramming (Shamis et al., 2012).

Three-dimensional cultures can also be exploited for CD-ECM production. It is known that aggregation of MSCs into spheroids leads to elevated expression and secretion of paracrine factors; spheroids treatment with macromolecular crowders accelerating deposition of ECM and accumulation of secreted factors followed by decellularization allowed to produce 3D-scaffold promoting cell adhesion and proliferation

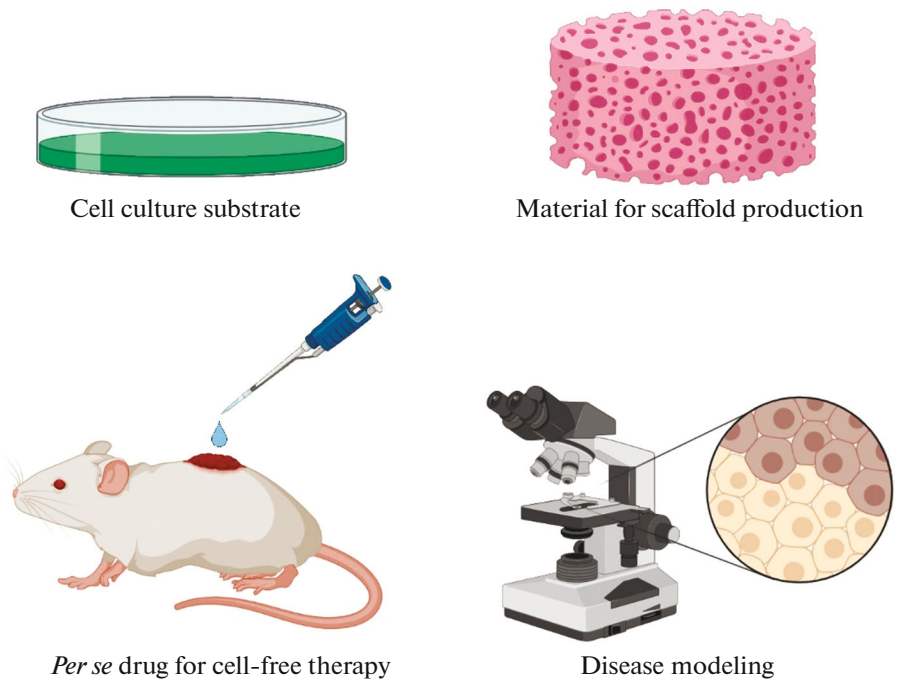

Fig. 2. CD-ECM potential uses. Created on BioRender.com

as well as the in vivo angiogenesis (Chiang et al., 2021).

Another approach to ECM customization is co-culture. Mixed fibroblasts and osteoblasts were demonstrated to deposit ECM that stimulated osteogenic differentiation in vitro and promoted bone regeneration in vivo better than matrices produced by fibroblasts and osteoblasts each separately (Li et al., 2020). CD-ECM composition is also influenced by culture conditions (Matveeva and Andreeva, 2020); thus, MSCs cultured in chondroinductive medium secrete ECM that mimics microenvironment of early chondrogenesis stage, and such ECM was used for production of hydrogel supporting chondrogenesis and hyaline cartilage formation in vivo (Antich et al., 2021). Besides, CD-ECM can be equipped with additional functional groups directly during the culture: thus, cells cultured in medium supplemented with modified monosaccharide produced an ECM functionalized with azide groups; such ECM can easily be covalently bound with antibiotics, growth factors or other molecules with use of bioorthogonal azide-alkyne cycloaddition ("click" reaction) (Ruff et al., 2017). Cells cultured on surfaces with specific nanotopography were shown to deposit ECM significantly affecting genes expression (including upregulation of chondrogenesis-related genes) in cells seeded on such nanopatterned ECM (Ozguldez et al., 2018).

Disadvantages

Discussing CD-ECM disadvantages, it should first be stressed that, compared to organ- and tissue-derived ECMs, cells produce very small amounts of ECM, so production of CD-ECM should massively be scaled up if it is meant to be used for biomedical applications. Large-scale culture brings a variety of challenges such as need for appropriate facilities (automated cell culture systems, biobanks), standardization of culture protocols, media, supplements and cell lines producing ECM; surely, proper equipment and large-scale cell culture itself require substantial financial costs. Nonetheless, development of the optimized scaling technology would allow to produce ECM of desired composition and unlimited quantities (Chan et al., 2021). Some approaches are suggested for stimulation of CD-ECM deposition, such as hypoxia culture conditions (Gilkes et al., 2013; Du et al., 2017), macromolecular crowders (Marinkovic et al., 2021) and matrix metallopeptidase inhibitors as medium supplements (Han et al., 2016).

In addition, CD-ECM are inferior in mechanical properties to native tissues. Among the approaches to overcoming this drawback, mention may be made of the introduction of crosslinking agents into CD-ECM (Nyambat et al., 2020); combining synthetic polymers that possess necessary mechanical properties with CD-ECM that provides specific biological activities can also be a potential solution. Thus, a polycaprolactone scaffold was modified with ECM of co-cultured MSCs and endothelium of umbilical vein (HUVEC); this composite did not lose its mechanical properties

and was shown to promote proliferation and osteogenic differentiation (Carvalho et al., 2019).

POTENTIAL OF USING CD-ECM

Cell Culture Substrate

Obviously, routinely used tissue/cell culture plastic is physiologically irrelevant. ECM significantly influences cell physiology in vivo, since it has optimal stiffness, regulates cellular polarity and forms specific microenvironment. Deprived of natural conditions, cells in culture manifest chromosomal aberrations, lose ability to differentiate and undergo premature senescence. These challenges can be exhibited during large-scale in vitro cell expansion for therapeutic use, as cells are grown for several passages. Compared to plastic, CD-ECM appears to be more physiological culture substrate. In a number of works it was shown that CD-ECM promotes proliferation and migration (Lin et al., 2012) and upregulates associated genes (Ragelle et al., 2017), maintains differentiation capacity (Lai et al., 2010), supports differentiation towards few lineages (Rao Pattabhi et al., 2014; Novoseletskaya et al., 2020), rejuvenates cultured cells (Choi et al., 2011; Joergensen and Rattan, 2014) and protects from H2O2-induced senescence (Yu et al., 2019). CD-ECM can also be used as feeder-free culture system for iPSC and embryonic stem cells (ESC). Widely used for this purpose commercially available substrate Matrigel is actually ECM produced by murine sarcoma cell line; it was also shown that other CD-ECM matrices can be used as substrate for iPSC, such as produced by human choriosarcoma cell line and dental pulp MSCs (Vuoristo et al., 2013; Chen et al., 2015).

Using in Tissue Engineering and Regenerative Medicine

In a number of studies it was shown that CD-ECM is an promising material for bone (Cheng et al., 2014; Junka and Yu, 2020; Li et al., 2020; He et al., 2021), cartilage (Antich et al., 2021; Dikina et al., 2017; Tang et al., 2019; Zhu et al., 2021) and skeletal muscle engineering (Zhang et al., 2020); MSCs are often used as ECM source for these purposes. Fibroblast-produced ECM was used for developing the composite vascular grafts (L'Heureux et al., 2006), heart valves (Weber et al., 2013) and scaffold for post-infarct cell therapy (Kim et al., 2019). CD-ECM can potentially be used in regenerative endodontics (Aksel et al., 2022).

CD-ECM can be used not only as a basis for creating scaffolds that deliver cultured cells into patients, but it may be implicated as *per se* drug that promotes regeneration by activation of resident cells. Proteomic analysis revealed that CD-ECMs contain proteins regulating immune processes, proliferation, differentiation, migration, adhesion and angiogenesis (Ragelle et al., 2017; Li et al., 2020); therapeutic effects of ECM applied to injured tissues is apparently related to ECM degradation and release of its bioactive components (Lee et al., 2019). In this regard, the use of ECM can be considered as a kind of cell-free therapy. Thus, ECMs of astrocytes and neural stem cells were demonstrated to promote spinal cord regeneration (Thompson et al., 2018; Chen et al., 2022); Schwann cell-derived ECM was able to restore injured nerves (Gu et al., 2014); ECMs produced by bone marrow MSCs and adipose tissue MSCs were shown to have wound healing properties (Du et al., 2017; Lee et al., 2019); it was patented a scaffold based on cardiac fibroblasts ECM that can be used for both cell delivery and as therapeutic itself for treatment of ischemic disease (Schmuck and Raval, 2016). It was also patented method for preparing biomaterial based on cell-free matrix produced by adipose tissue MSCs that can be used to stimulate regenerative processes (Nimiritskiy et al., 2016; Tkachuk et al., 2020).

Disease Modeling

It is known that many pathological states (neurodegenerative diseases, tumors, osteoarthritis, fibrosis, etc.) are accompanied with abnormal ECM remodelling, including quantitative and qualitative alterations of ECM composition, rearrangement of native tissue architectonics, impairment of dynamic equilibrium between degradation and synthesis of ECM, changes in ECM stiffness (Sonbol, 2018; Theocharis et al., 2019). Since ECM comprehensively controls cell functions, abnormal ECM remodelling violates tissue homeostasis and aggravates the course of the disease. Thus, the establishment of the ECM role in pathogenesis can result in development of new diagnostic methods or in discovery of therapeutic targets (Rubi-Sans et al., 2020). In this regard, ECM is of interest as component of cancer niche that promotes tumor progression and metastasis (Xiong and Xu, 2016). Along with ECM of malignant tissues, CD-ECM deposited by cancer cell lines is used as model for studying tumor microenvironment; although CD-ECM alone can not fully reproduce microenvironment of tumor tissue, it is considered to be methodologically convenient and scalable model for in vitro studies (Hoshiba, 2019). CD-ECMs are used for developing three-dimensional artificial tumors (Malakpour-Permlid et al., 2021); thus, the macroscopic (>1 cm) 3D tumor model based on PLA scaffold modified with ECM deposited by adipose tissue MSCs was similar in fibrillar structure and mechanical properties to tumor tissue and this model increased cancer cells resistance to doxorubicin (Rubi-Sans et al., 2021). ECM secreted by human trabecular meshwork cells (HTMC) was used to study the ECM role in glaucoma (Raghunathan, 2018). The microfluidic device was modified with fibroblast-derived ECM (Hong et al., 2017), and such approach can be utilized in production of organs-on-chips for consideration of ECM influences in disease modelling or in drug screening.

CONCLUSIONS

Cell cultures present an attractive alternative to traditional ECM sources, such as tissues and organs. The main benefit of CD-ECM is in vitro customization ability that is backed up by a rich methodological arsenal of cell biology and other domains of knowledge. Recent publications demonstrate that CD-ECM can potentially find broad biomedical application. Nevertheless, studies related to CD-ECM are still limited to cell and animal models. Apparently, the transition to clinical trials is constrained by low CD-ECM yield, so the CD-ECM translation into the clinic will require solving the scaling issue.

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COMPLIANCE WITH ETHICAL STANDARDS

The author declares no conflicts of interest. This article does not contain any studies involving animals or human participants.

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