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REVIEW

Potential of mesenchymal stem cells for bioengineered blood vessels in comparison with other eligible cell sources

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Abstract

Application of stem cells in tissue engineering has proved to be effective in many cases due to great proliferation and differentiation potentials as well as possible paracrine effects of these cells. Human mesenchymal stem cells (MSCs) are recognized as a valuable source for vascular tissue engineering, which requires endothelial and perivascular cells. The goal of this review is to survey the potential of MSCs for engineering functional blood vessels in comparison with other cell types including bone marrow mononuclear cells, endothelial precursor cells, differentiated adult autologous smooth muscle cells, autologous endothelial cells, embryonic stem cells, and induced pluripotent stem cells. In conclusion, MSCs represent a preference in making autologous tissue-engineered vascular grafts (TEVGs) as well as off-the-shelf TEVGs for emergency vascular surgery cases.

Keywords Mesenchymal stem cells · Tissue engineering · Vascular grafting · TEVGs · Vascular diseases

Introduction

The vascular system in the human body is exposed to various kinds of diseases, including cardiovascular, cerebrovascular, and peripheral vascular diseases. Cardiovascular diseases constitute a common and great problem in both developed and developing countries (Bhatnagar, et al., 2015, Sadeghi, et al., 2017). According to the report of the World Health Organization (WHO) in 2017, cardiovascular problems take the lives of 17.7 million people every year, which is 31% of all global deaths. Cardiovascular diseases (CVDs) include coronary heart disease (CHD) and coronary artery disease (CAD), and acute coronary syndrome (ACS) (Sanchis-Gomar, et al., 2016). Cerebrovascular diseases include stroke, aneurysm, blood vessel rupture (hemorrhage), and clot formation (thrombosis) in the brain (Members, et al., 2012). Peripheral vascular diseases (PVDs) are blood circulation disorders that result in narrowing, blockage, or spasm of blood vessels outside the heart and brain. This can happen in arteries or veins affecting the blood and oxygen supply to the arms, stomach, and kidneys (DeLoach and Mohler, 2007, Hess and Hiatt, 2018).

Using grafts (autografts, allografts, and prosthetic grafts) is one of the common ways in treating vascular diseases. Suitable vessel grafts should have specific properties such as low thrombogenicity, biocompatibility, and be usable for a variety of lengths. Furthermore, these grafts must resist physiological pressures without leakage or aneurysm formation and should not elicit an immunological response in the patient (Gong and Niklason, 2008).

All mentioned grafting methods have their own disadvantages and limitations. Therefore, there is a consensus among scientists on the importance of developing alternative therapeutic methods. Among these, tissue engineering is a preferred approach, which can open a new window in the treatment of vascular diseases. Tissue engineering addresses the use of cells, scaffolds, and growth factors for making whole or part of tissues such as the bladder (Ambasta et al., 2017), cartilage (Zhang et al., 2009), and skin (Boyce and Lalley, 2018). Recent progress in this field is conducted with stem cells because of the high self-renewal, proliferation, and differentiation capacities of these cells (Vacanti, 2006). This paper summarizes the application of mesenchymal stem cells in

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tissue-engineered vascular grafts (TEVGs). In addition, we compared the potential of mesenchymal stem cells in the treatment of vascular diseases with other types of eligible cells, including bone marrow mononuclear cells, endothelial precursor cells, autologous endothelial cells (ECs), and smooth muscle cells (SMCs), which are eligible adult differentiated cells, as well as embryonic stem cells, and induced pluripotent stem cells (iPSCs).

Different methods in vascular grafting

Vascular grafting can be best classified into five categories: I, autografting; II, cryopreserved allografting; III, prosthetic grafts; IV, decellularized vascular scaffolds; and V, tissue engineering using stem cells. The first four options are now clinically in use and the last one is under progress. The common method in the treatment of CVDs is coronary artery bypass grafting. There are two main approaches, internal thoracic artery (ITA) grafts and autologous saphenous vein grafts (SVGs), which are the gold standard treatments for coronary bypass and lower limb arterial bypass, respectively (Baguneid, et al., 2006, Karthik and Fabri, 2006). Bypass surgery has been in use for many years but is still facing major problems, which have not been solved yet. One drawback with SVG is the low patency which is 70–75%, for 5 years (Baguneid et al., 2006). ITA grafts have demonstrated better patency than SVGs, but there are some postoperative complications in the harvesting of the ITA and also the invasive aspect of both mentioned methods cannot be disregarded (Leavitt, 2004, Sabik III, et al., 2005). Although these surgeries are mainstay methods of revascularization for CVDs, approximately 30% of patients do not have suitable vessels for autografting (Hsia, et al., 2016).

An alternative method is using allografts. Allograft cryopreserved saphenous veins are used when the autologous one is insufficient or unavailable, and thus, blood vessel banks are essential. The advantage of this method is keeping vessels in subzero temperatures and saving them for a long time; however, freezing and defrosting could damage tissues and cells, especially endothelial cells which have a great influence on patency and success rates of surgeries (Müller-Schweinitzer, 2009). In addition, finding suitable grafts, which have similar expressed proteins to the patient for reducing immunogenic responses, is difficult. In a study conducted by Farber et al., low patency of cryografts in 240 patients was reported (Farber, et al., 2003). Another study clinically surveyed the cryopreserved saphenous vein allograft's capacity for infrainguinal bypass, among 53 patients. The maintained patency was 1 year in 53% of patients and 3 years in 22% of patients, with 2 deaths, 8 thromboses, 2 amputations, and 1 anastomotic disruption. Fifteen patients had additional operations with the use of synthetic conduits. As the authors concluded, their study on cryopreserved allografts with long-term period follow-ups showed no acceptable outcome (Hartranft, et al., 2014). Poor long-term or short-term patency, risk of infection, immunogenic response, and not responding to the anticoagulation agents indicate that cryopreserved saphenous vein allograft is suboptimal with lower quality in comparison with other conduits in surgical fields (Farber, et al., 2003, Hartranft, et al., 2014, Randon, et al., 2010, Vogt, et al., 2002, Walker, et al., 1993).

There are available prosthetic materials such as expanded polytetrafluoroethylene (ePTFE) and polyethylene terephthalate (also referred by the brand name Dacron) with approximately 40–50% patency for 4 years (Camiade, et al., 2003, Glickman, et al., 2002, How, 1992, Weinberg and Bell, 1986). Although synthetic grafts have unlimited availability, these conduits with a small diameter (less than 6 nm) have less patency compared with autografts and the rate of thrombosis is too high (Desai, et al., 2011, Kannan, et al., 2005). There are also some reports suggesting that materials of these prosthetic grafts can provide niches for bacterial accumulation (Shell IV, et al., 2005). Although prosthetic vascular graft infection is uncommon, but if it happens, it would be severe, and lead to revision surgery (Keidar, et al., 2007, Kirkton, et al., 2018). In addition, prosthetic materials do not respond to their environment and do not have the ability of self-repairing so they will not achieve essential tissue ingrowth to be covered by endothelium and/or smooth muscle cells (Baguneid, et al., 2006) (Fig. 1).

Use of acellular biological scaffolds as vascular conduits was first proposed by Rosenberg et al. who used a tanned bovine carotid artery in human (Rosenberg, et al., 1966). Decellularized vascular scaffolds could have human allogeneic or xenogeneic sources (Lin, et al., 2018). Because of the absence of cells, the immunogenic rejection is not expected but the extracellular matrix (ECM) must compensate for mechanical properties which are provided by cells in natural vessels. After implantation in the body, the ECM plays a major role in induction or regeneration of cells (2–8 weeks). These grafts are currently in the market, some of which include the Artegraft, Solcograft from a bovine carotid artery, ProCol from a bovine vein, and SynerGraft from a bovine ureter, which are clinically in use. The most important advantage of acellular vascular grafts is their availability and saving time in emergency cases, but both xenogeneic and human allogeneic types of acellular grafts have their own problems. Decellularized xenogeneic grafts have a higher cost in comparison with prosthetic grafts and also did not show large-scale adoption. Several studies offered no

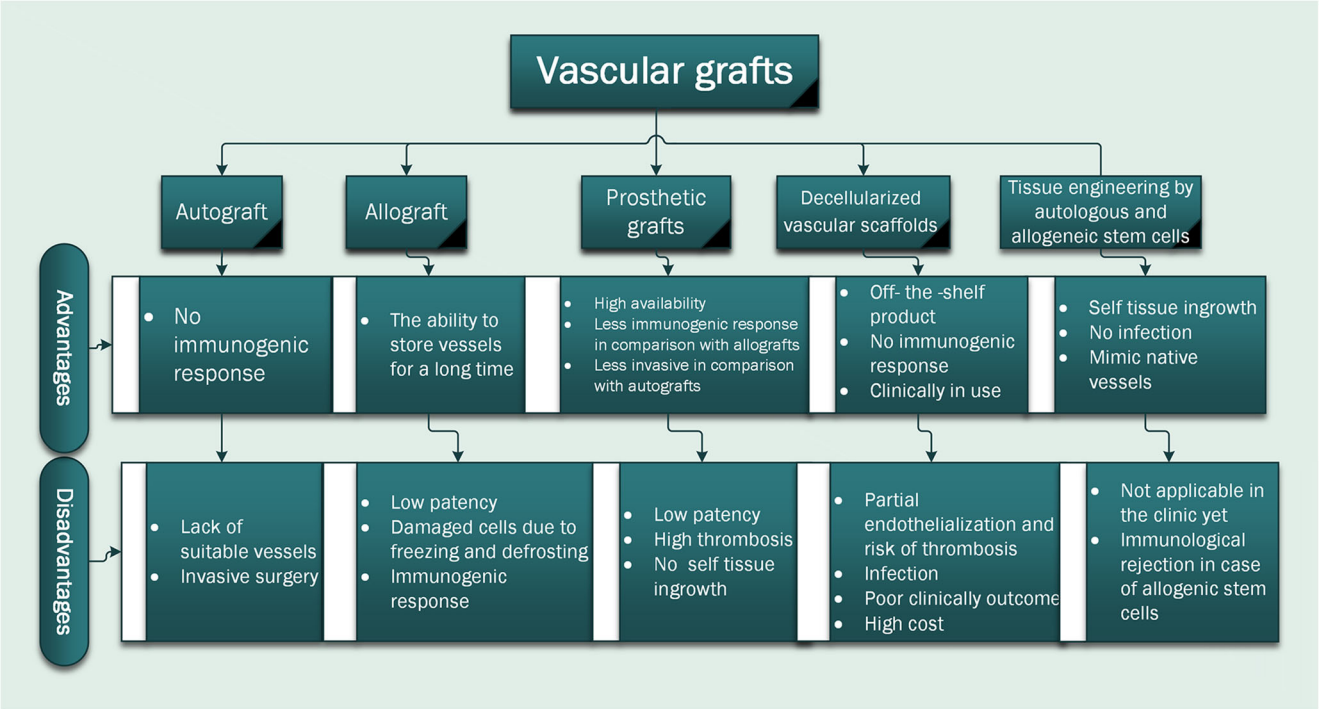

Fig. 1 Different methods in vascular grafting

preference in using decellularized xenogeneic grafts in comparison with prosthetic grafts especially in hemodialysis grafts (Berardinelli, 2006, Chemla and Morsy, 2009, Li, et al., 2008). In addition, thrombosis, infection, and aneurysm formation were reported in connection with using these xenografts (Chemla and Morsy, 2009, Olausson, et al., 2014). In the case of using decellularized human vessels, a major problem is availability of human donors as well as ethical and regulatory issues associated with commercialization of such products (Pashneh-Tala, et al., 2015). Although both types of acellular grafts eliminate the need for isolating autologous cells for seeding, partial endothelialization and remodeling (which is necessary for maintaining patency) have been reported (Martin, et al., 2005). Adding growth factors could increase the speed of endothelialization, but as reviewed by Lin et al., the longest period, in which the decellularized vessels had high patency, was 14 months (Lin, et al., 2018, Sakakibara, et al., 2014). Considering the effects of different preparation methods to achieve acellular grafts, the highest duration of patent vessels (14 months) is not comparable with 4-year patency in allografting as a gold standard for treatment of CVDs. Some studies use recellularization of decellularized scaffolds. In this approach, the risk for immune rejection of allogeneic cells and the possibility of autologous cell senescence as well as the long culture time in bioreactors are indispensable (Lin, et al., 2018). In addition, in the case of recellularization, we are back to the first question, "What is the best cell source for vascular regeneration?" as is discussed in the rest of this review. Overall, more studies are required to enhance desired properties of decellularized vascular scaffolds and overcome current disadvantages (Fig. 1).

The last method in vascular grafting is tissue engineering using stem cells; one of the major attempts in this subject is tissue-engineered vascular grafts (TEVGs) (Krawiec and Vorp, 2012). Essential parameters for TEVGs can best be discussed under three major headings: the scaffold, the required growth factors, and the cells (endothelial cells (ECs) and smooth muscle cells (SMCs)). There are many reports using these grafts in animal models with maintaining antithrombogenic aspect (Hoerstrup, et al., 2006, L'Heureux et al., 2006, Roh, et al., 2010). TEVGs are also used in human clinical trials but still, no clinical and commercial applications are reported. The results of using TEVGs into the clinical trials showed no evidence of severe problems (Hibino, et al., 2010, Sugiura, et al., 2018, Wystrychowski, et al., 2014). More clinical trials are in progress to investigate the possibility of using TEVGs for clinical and off-the-shelf applications (L'Heureux et al., 2007, Ong, et al., 2017) (Fig. 2).

Considering the high rate of vascular diseases and the limitations of current methods, there is a great need for alternative conduits to fulfill the properties of ideal vessel grafts. Therefore, tissue-engineered vessels, especially using stem cells, could be a new and reasonable solution in this regard.

The potential of eligible cell sources for making TEVGs will be discussed in the next section.

Mesenchymal stem cells in comparison with other eligible cells in TEVGs

Mesenchymal stem cells (MSCs), bone marrow mononuclear cells (BM-MNCs), endothelial precursor cells (EPCs), autologous endothelial cells (ECs), autologous smooth muscle cells (SMCs), embryonic stem cells (ES), and induced pluripotent stem cells (iPSCs) can be used in TEVGs. In this section, the potential of MSCs in vascular regeneration is compared with other eligible cell types to clarify the merits of these cells.

MSCs are adherent adult stem cells, with high proliferation and differentiation potency. These cells can be derived from many sources including adipose tissue, bone marrow, cord blood, liver, and spleen (Bahrami, et al., 2011, Huang and Li, 2008, Neshati, et al., 2010). There are many studies demonstrating the multi-lineage potential of MSCs to differentiate into cell types of mesodermal origin such as adipocytes, osteoblasts, and chondrocytes (Wang, et al., 2012). Specific markers can be used for characterization of these cells including STRO-1 (a stromal cell surface antigen), CD29 (Integrin β1), CD44 (receptor for hyaluronic acid and matrix proteins), CD105 (endoglin), and CD166 (cell adhesion molecule). MSCs can secrete a wide spectrum of bioactive macromolecules, which can regenerate a better environment in injured tissues and inhibit inflammation (Shoji and Shinoka, 2018). Caplan referred to the homing property of MSCs and their participation in injury response by producing various paracrine factors as their "trophic activity" in regenerative medicine (Caplan, 2007). Coupling both tissue engineering capacity and the trophic activity of MSCs could be used massively in tissue regeneration. MSCs have immunomodulatory properties, including suppression of T cells (Di Nicola et al., 2002, Corcione et al., 2006), immune modulation of natural killer cells (NK) (Sotiropoulou et al., 2006), and macrophages (Yi and Song, 2012; Mathieu et al., 2009).

Comparison with bone marrow mononuclear stem cells

BM-MNCs are another rich source of stem cells including endothelial precursor cells (EPCs), MSCs, hematopoietic stem cells, and also monocytes, $CD4^+$ T cells, $CD8^+$ T cells, B cells, and NK cells (Roh, et al., 2010). The ability of these cells to differentiate into SMCs and endothelial-like cells is reviewed by Krawiec and Vorp (2012).

Some scientists infer to the role of monocytes in a mixed population of BM-MNCs, which can maintain the patency of the vessel, and it could be considered as a merit for using BM-MNCs in comparison with MSCs in TEVGs. MSCs require weeks of passage in culture, but they carry a wider therapeutic window compared with BM-MNCs by a higher expansion rate of over 1 million-fold and maintaining multi-lineage differentiation capacity (Mir and Savitz, 2013). On the other hand, because of the presence of B and T cells in BM-MNCs, they induce immunogenic responses and should be used from autologous sources, but another concern about BM-MNCs is that they can differentiate into a variety of mature cells and are not lineage specific for ECs and SMCs (Wang, et al., 2016). BM-MNCs have been successfully used in human TEVG clinical trials, and no evidence of aneurysm formation, graft rupture, and graft infection was detected (Hibino, et al., 2010, Sugiura, et al., 2018). Although using TEVGs, made of BM-MNCs, had successful results in clinical trials, further clinical studies are still necessary (Wang, et al., 2016).

Both MSCs and BM-MNCs have their own advantages and disadvantages. As shown in Table 1, the immunogenic response is the major problem with BM-MNCs, especially in allografts.

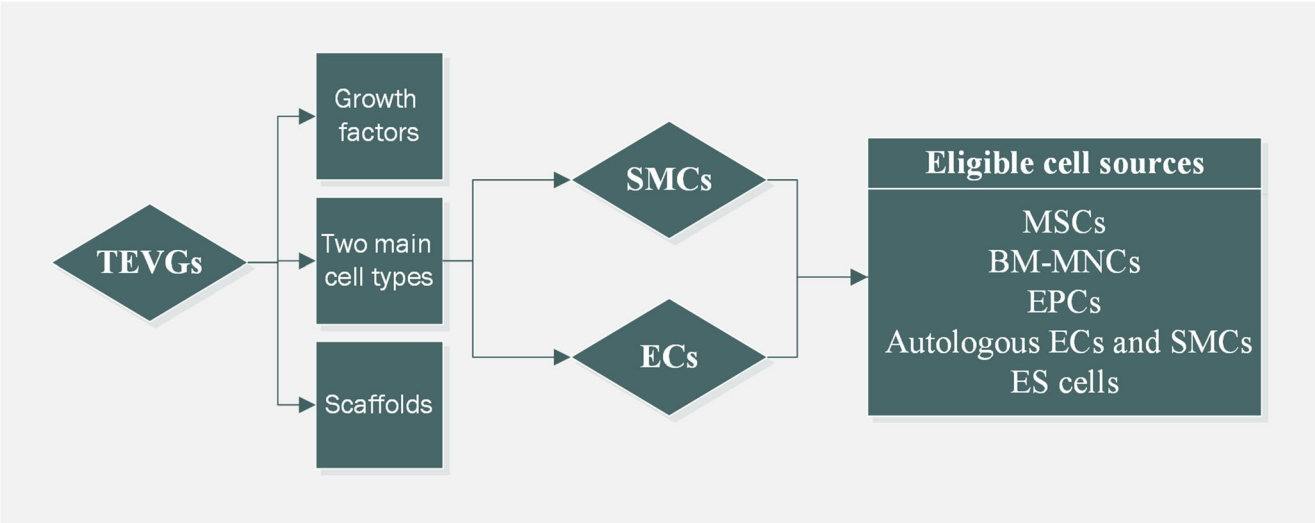

Fig. 2 Tissue engineering vascular grafts. TEVGs tissue-engineered vascular grafts, SMCs smooth muscle cells, ECs endothelial cells, MSCs mesenchymal stem cells, BM-MNCs bone marrow mononuclear cells, EPCs endothelial precursor cells, and ES cells embryonic stem cells

Table 1 Mesenchymal stem cells in comparison with other eligible cell types in TEVGs

Cell source	Advantages	Disadvantages
MSCs	▪ Immunomodulatory effects (Di Nicola, et al., 2002, Yi and Song, 2012) ▪ Both autografting and allografting capacity (Salem and Thiemermann, 2010) ▪ Homing (Caplan, 2007,Heirani-Tabasi, et al., 2018) ▪ Different sources of harvesting (Huang and Li, 2008) ▪ Noninvasive methods for isolation including liposuction (Zuk, et al., 2002) ▪ Multipotent stem cells (Neshati, et al., 2010, Tobiasch, 2009) ▪ No detectable teratoma formation (Hielscher, et al., 2018)	▪ Require weeks of passage in culture (Mir and Savitz, 2013)
BM-MNCs	▪ Good effects on maintaining patency of the vessels (antithrombogenic effects) (Mathieu, et al., 2009, Mir and Savitz, 2013) ▪ Include EPCs (Roh, et al., 2010) ▪ Proven safety and feasibility in clinical trials (Hibino, et al., 2010, Sugiura, et al., 2018)	▪ Immunogenic responses (Krawiec and Vorp, 2012, Roh, et al., 2010)
EPCs	▪ Easy harvesting from blood circulation (Ambasta, et al., 2017, Brunt, et al., 2007)	▪ Unipotent stem cells ▪ Not differentiating to SMCs (Ladhoff, et al., 2010)
Autologous ECs and SMCs	▪ No immunogenic response	▪ Invasive harvesting ▪ Low proliferation ability (Zhang, et al., 2009)
ES cells	▪ Pluripotent stem cells (Gan, et al., 2003, Riha, et al., 2005, Thomson, et al., 1998) ▪ High proliferation ability (Ruiz, et al., 2011)	▪ Ethical problems (Kimmelman, et al., 2016) ▪ Tumor formation (Hentze, et al., 2009, Wang, et al., 2017) ▪ Immunogenic rejection (Leeper et al., 2010)
iPSCs	▪ Pluripotent stem cells (Yamanaka, 2007) ▪ High proliferation ability ▪ Low risk of immunogenic response (Cao, et al., 2014) ▪ No ethical problems	▪ Time-consuming ▪ High cost ▪ Teratoma formation

MSCs mesenchymal stem cells, *BM-MNCs* bone marrow mononuclear cells, *EPCs* endothelial precursor cells, *ECs* endothelial cells, *SMCs* smooth muscle cells, and *ES* embryonic stem cells

Comparison with endothelial precursor cells

Endothelial precursor cells (EPCs) are unipotent stem cells with the ability of differentiation into endothelial cells. They are isolated from mononuclear fraction and could be classified into early- and late-outgrowth EPCs with a great impact on angiogenesis (Asahara, et al., 1997, Ladhoff, et al., 2010). EPCs are present in blood circulation at different stages of differentiation (Brunt, et al., 2007) proposing a very good supply of autologous ECs. Harvesting EPCs from peripheral blood (PB-EPCs) is less invasive than harvesting MSCs from the bone marrow or adipose tissue. PB-EPCs could be mobilized from the bone marrow into circulation using cytokine drugs and hormones (Ambasta, et al., 2017) and could be enriched using endothelial cell-growth factors. However, the presence of MSCs in circulating blood is debated and the results are not always reproducible (Riha, et al., 2005, Roufosse, et al., 2004). Late-outgrowth EPCs express a low level of MHC class I and similar to MSCs do not express MHC class II molecules. Hence, their low ability to make immunogenic response could be considered as a preferred property, but these cells are unipotent and cannot differentiate to SMCs. Co-culture of MSCs/EPCs showed a significant rise in vascularization (Hjortnaes, et al., 2009, Seebach, et al., 2010).

These data showed that EPCs are an ideal cell source for achieving mature ECs but it is clear that they must be used in combination with other cell types capable of differentiation into SMCs in order to make functional TEVGs.

Comparison with autologous endothelial cells and smooth muscle cells

Two important types of cells, which are required for vascular regeneration, are ECs and SMCs. In fact, the first option for making TEVGs is autologous ECs and SMCs isolated from

patients themselves with no immune response, which requires patient-specific cell isolation. Although ECs, SMCs, and fibroblasts could be isolated from a single and small vein biopsy (Grenier, et al., 2003), it is an invasive treatment strategy and there is no guarantee for maintaining and growing these cells in vitro. These differentiated cells have a very low proliferation ability and the chance of having sufficient cell numbers for making TEVGs is almost equal to zero. To date, there is no developmental solution for proliferation deficiency of these cells (Zhang, et al., 2009). A reasonable approach to tackle this issue is finding alternative cell sources which necessitate the use of stem cells with renewal, proliferation, and differentiation capacity.

Comparison with embryonic stem cells

Stem cells, according to their origin, can be classified into embryonic stem cells and adult stem cells. The first merit of embryonic stem cells, as a cell source for the goal of tissue regeneration, is their ability to produce all kinds of cells which is considered as pluripotency as well as greater proliferative capacity in comparison with adult stem cells. Since mouse and human pluripotent embryonic stem (ES) cells have been successfully established from blastocysts in 1981 and 1998, respectively (Martin, 1981, Thomson, et al., 1998), a considerable literature has reported differentiation ability of ES cells into ECs and SMCs. The procedure could be controlled by using growth factors, cytokines, or conditioned medium (Gan, et al., 2003, Huang, et al., 2006, Nie, et al., 2017).

The problem of using ES for various areas of tissue engineering is the risk of tumor formation (Hentze, et al., 2009) besides ethical problems surrounding the use of human embryos for derivation of these cells. ES cells derived from inner cell mass would be allogeneic and require administration of immunosuppressive agents to avoid immune rejection. Although clinical trials using ES cells are increasing, the mentioned issues are debatable (Kimmelman, et al., 2016, Leeper, et al., 2010).

Comparison with induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) can be produced directly from adult differentiated cells and have the pluripotency aspect similar to ES cells without the need for embryos and inner cell mass. The phrase, induced pluripotent stem cells, was first used in the article of Yamanaka and his colleague, who made iPSCs by special transcription factors (Takahashi and Yamanaka, 2006). Before that, pluripotent cells could be generated by somatic cell nuclear transfer into oocytes (Wilmut, et al., 1997) and somatic cell fusion with ES cells (Cowan, et al., 2005, Tada, et al., 2001). In all the mentioned methods, nuclear DNA of a somatic cell could be "reprogrammed" to express genes involved in pluripotency. Human iPSCs can be generated from accessible tissues such as skin, fat, or hair, and they can be highly expanded in vitro. Therefore, iPSCs provide unlimited autologous pluripotent cells for regenerative medicine without ethical problems. One of the restrictions associated with these cells is retroviral or lentiviral transduction. This viral vectors could raise the risk of silencing indispensable genes and/or inducing oncogenesis (Okita, et al., 2007). In addition, there is the risk of DNA integration when these viruses or plasmid constructs are used. Recently, integration-free reprogramming methods, such as episomal vectors, piggyBac transposon, proteins, viral non-integrating method (Sendai virus), and miRNAs, were developed to reduce the risk of chromosomal integrations or breaks (Abou-Saleh, et al., 2018, Fusaki, et al., 2009, Hou, et al., 2013, Okita, et al., 2008, Woltjen, et al., 2009, Ye and Wang, 2018). Another problem is an animal source of feeder layer which is used during hiPSC culture (Takahashi and Yamanaka, 2006). Feeder layer with the human origin is an alternative solution, but preparation of these cells is time-consuming. For generation of hiPSCs without xenogeneic components, other types of matrices including Matrigel, recombinant proteins, and synthetic polymers have been examined. Developing non-xenogeneic or feeder-free conditions is continued (Seki and Fukuda, 2015).

For making TEVGs from hiPSCs, they must grow in specific culture conditions in order to differentiate into vascular smooth muscle cells (Gui, et al., 2016), mesenchymal cells (Sundaram, et al., 2014), mesenchymal precursor cells, and endothelial precursor cells (Samuel, et al., 2013, Wu, et al., 2010). Culture media must contain specific inducers to direct hiPSCs to vascular cells while preventing the possibility of teratoma formation (Leeper et al., 2010).

Since hiPSCs are derived from a person's own somatic cells, an immunogenic response in not expected, however, a study in 2014 showed that in some cases cells derived from mouse iPSCs could be immunogenic (Cao, et al., 2014). Another concern is the time required for generating TEVGs from iPSCs which requires two steps: generation of iPSCs followed by differentiation into vascular precursor cells (2 months and 21 days to make implantable TEVGs (Gui et al., 2016)). Although new methodologies can increase the yield of reprogramming and decrease the preparation time (Kogut, et al., 2018, Papapetrou, 2016, Ye and Wang, 2018), the high costs for the therapy might mean it would be seldom applicable to large numbers of people (Nishikawa et al., 2008). To compare MSCs and hiPSCs, both could easily be harvested from adipose tissues and both require weeks of passages to make vascular cells, but using MSCs in TEVGs does not face the risk of teratoma formation. As it was reviewed before by Leeper et al., hiPSCs were shown to have the greatest promise for vascular regeneration in comparison with some adult stem cells (EPCs in particular) (Leeper, et al., 2010), but making

TEVGs from hiPSCs needs to overcome tumorigenesis and establish effective differentiation methods into vascular cells. Thus, while iPSCs have an important role in regenerative medicine, the high cost and risk of teratoma formation cannot be ignored. Therefore, there is not any obvious seductive preference for using hiPSCs in comparison with MSCs especially in emergency cases, and both cell types would benefit from improved methodologies to decrease the required culture time.

In summary, comparing the use of MSCs for TEVGs with four major eligible cells indicates that there are some unsolved problems associated with using other cell types. It is not possible to reach sufficient cells from autologous ECs and SMCs. EPCs cannot make a complete vessel without the presence of another cell source for SMCs. Although various studies are being developed to use ES cells for vascular tissue engineering in animal models, the functionality of such ES-derived cells in engineering human vascular grafts still remains to be tested (Wang, et al., 2017). In the case of using hiPSCs, developing strategies to overcome teratoma formation is essential. Thus, MSCs have some preferences over other cell types to be used in TEVGs. Moreover, they have more advantages for making TEVGs compared with BM-MNCs, however, since they have not been in use in clinical trials yet (there are two completed clinical trials for BM-MNCs) (Hibino, et al., 2010, Sugiura, et al., 2018), it is difficult to make a conclusion. The most obvious disadvantage of BM-MNCs is eliciting an immune response in allografts. Therefore, BM-MNCs are not an ideal option for off-the-shelf TEVGs.

In general, there are many unanswered questions surrounding the best cell sources in regenerative medicine and the best solution would be related to the disease and physical conditions of the patients.

Differentiation of mesenchymal stem cells to endothelial cells

In general, MSCs are derived from the mesoderm and could be differentiated to osteoblasts, chondrocytes, and myocytes but not directly to endothelial cells (ECs). The main origin of EC is endothelial precursor cell (EPC) which is derived from the bone marrow (Naderi, et al., 2011, Yoder, 2017); however, MSCs could also differentiate into endothelial cells in special conditions.

Various factors and culture conditions have been examined for their inducing effects on MSC differentiation into ECs. The factors, used for this purpose include VEGF (vascular endothelial growth factor), hypoxia condition, and hemodynamic forces (Abdollahi, et al., 2011, Gu, et al., 2009, Khaki, et al., 2018, Oswald, et al., 2004, Zhou, et al., 2016) which will be discussed as follows.

VEGF, also known as vascular permeability factor (VPF), was originally described as an endothelial cell-specific mitogen and has specific receptors on ECs. Low serum medium and VEGF as a supplementary factor are capable of differentiating MSCs to ECs in vitro. Under described conditions, MSCs acquired several features of mature endothelium, including the expression of VEGF receptors, VE-cadherin, VCAM-1, and von Willebrand factor (vWF) (Oswald, et al., 2004).

Hypoxia condition is another debatable factor affecting self-renewal, migration, differentiation, gene expression, and vascular tube formation of MSCs. Hypoxia appears to stimulate the expression of VEGF followed by more differentiation to mature endothelial cells (Abdollahi, et al., 2011, Han, et al., 2010). Another reason for the positive effects of hypoxia condition on successful neovascularization is nitric oxide. Nitric oxide production by differentiated ECs plays a critical role in thrombo resistance by inhibiting platelet adhesion. The level of nitric oxide is higher in hypoxia condition (1–5% O_2) in comparison with normoxia condition (10–21% normal O_2 level) (Zhou, et al., 2016).

Hemodynamic forces, including shear stress and cyclic strain, are important modulators of vascular functions and morphology (Kakisis, et al., 2004). Therefore, they can have a crucial impact on vascular engineering by stem cells. Shear stress naturally exists in human and animal vessels. The endothelium layer of arteries tolerates shear stress within the range of 10 to 20 dyn/cm^2 (Huang and Li, 2008). Dong et al. evaluated the implication of shear stress in TEVGs. They initiated the shear stress at 1 dyn/cm^2 on canine MSCs and observed a significant rise in expression of EC-specific markers at both mRNA and protein levels (Dong et al., 2009).

A combination of VEGF, laminar shear stress (LSS), and deferoxamine mesylate (DFX) has also been used to induce differentiation of MSCs to ECs. DFX is used especially for mimicking the hypoxia condition (Heirani-Tabasi, et al., 2018, Liu, et al., 2017).

In another study, hMSCs cultured in endothelial growth medium were subjected to shear stress and after 10 days, morphological changes, CD31, and vWF expression were detected (Portalska, et al., 2012).

With all pieces together, it is concluded that it would be possible to differentiate MSCs into ECs using various factors including VEGF, shear stress, and hypoxia condition (Table 2).

Differentiation of mesenchymal stem cells to smooth muscle cells

Studies have previously demonstrated the ability of MSC differentiation into different types of myocytes such as smooth

Table 2 Factors involved in differentiation of mesenchymal stem cells into endothelial cells

MSC differentiation to ECs	Induction factors	References
Human bone marrow MSCs	Low serum medium, VEGF	Oswald et al. (2004)
Canine bone marrow MSCs	Increasing shear stress	Gu et al. (2009)
hMSCs	Endothelial growth medium, shear stress	Portalska et al. (2012)
hAd-MSCs	VEGF, hypoxic conditions	Zhou et al. (2016)
Rat bone marrow MSCs	VEGF, laminar shear stress (LSS), deferoxamine mesylate as a hypoxia inducer	Liu et al. (2017)

VEGF vascular endothelial growth factor, *hAd-MSCs* human adipose-derived mesenchymal stem cells

muscle cells (SMCs). Scientists designed and examined different culture conditions by addition of specific growth factors such as TGF-β1 and also mechanical stress to increase MSC differentiation into SMCs as indicated in Table 3 (Hamilton, et al., 2004, Kurpinski, et al., 2010, Tamama, et al., 2008, Wakitani, et al., 1995).

Transforming growth factor-β1 (TGF-β1) is a cytokine with the ability to control proliferation and differentiation. This cytokine can promote the expression of alpha-smooth muscle actin (α-SMA) in myofibroblasts (Vaughan, et al., 2000) through the Notch pathway (Kurpinski, et al., 2010). It has been shown that adult rat MSCs have the potential to differentiate into SMCs when exposed to TGF-β1. Human MSCs also exhibited enhanced differentiation with increased contractility in response to TGF-β1 (Tamama, et al., 2008). Addition of 1 ng/ml TGF-β1 to the culture medium of hMSCs induced their differentiation into SMCs and basal level of α-SMA and Calponin expression (Gong and Niklason, 2008). Furthermore, it was shown that following a 1-week treatment with 5 ng/ml TGF-β1 and 2.5 ng/ml BMP4 hAD-MSCs could differentiate into SMCs. Phalloidin staining confirmed the formation of a fiber pattern similar to SMCs besides the positive immunofluorescent staining of α-SMA and Calponin in differentiated cells (Zhou et al., 2016; Wang et al., 2010).

So far, three main mechanical stimuli, including cyclic stretch, cyclic pressure, and laminar shear stress, have been applied independently in cultures to evaluate their effects on differentiation of MSCs into SMCs.

Kobayashi et al. demonstrated that mechanical stress could promote the expression of the smooth muscle cell-specific cytoskeleton proteins in marrow stromal cells. Fluid flow-induced mechanical forces (flow dominant, pressure dominant, or combined) improved α-SMA expression in treated cells (Kobayashi, et al., 2004).

Furthermore, MSC differentiation into SMCs was possible without adding growth factors and just by a combination of lineage-specific surface stiffness with cyclic stretch (Hamilton, et al., 2004) with higher expression of SMC proteins at 1 Hz (Maul, et al., 2011).

On the other hand, shear stress has a different effect on differentiation of MSCs to SMCs. As mentioned before,

Table 3 Factors involved in differentiation of mesenchymal stem cells into smooth muscle cells

MSC differentiation to SMCs	Induction factors	References
Rat bone marrow MSCs	Mechanical stress	Kobayashi et al. (2004)
Rat bone marrow MSCs	Cyclic stretch	Hamilton et al. (2004)
Human bone marrow MSCs	TGF-β1	Tamama et al. (2008)
Human bone marrow MSCs	TGF-β1	Gong and Niklason (2008)
hAd-MSCs	TGF-β1, BMP4	Wang et al. (2010)
hAd-MSCs	TGF-β1, BMP4	Zhou et al. (2016)
Human bone marrow MSCs	Cyclic stretch	Ghazanfari et al. (2009)
hUC-MSCs	miR-503 and miR-222-5p	Gu et al. (2018)

TGF-β1 transforming growth factor-β1, *hAd-MSCs* human adipose-derived mesenchymal stem cells, *hUC-MSCs* human umbilical cord mesenchymal stem cells

shear stress could increase differentiation of MSCs to ECs but it substantially decreased expression levels of α-SMA as investigated by Gu et al. (2009) or had no significant effect on SMA or calponin expression as shown by Maul and colleagues. In addition, the duration of shear stress until 72 h decreased muscle phenotype, whereas cyclic strain increased muscle differentiation (Maul, et al., 2011). This is similar to the findings of Ghazanfari et al. who proved the positive impact of cyclic stress in the differentiation of hBM-MSCs to SMCs (Ghazanfari, et al., 2009).

Of note, the microRNA (miR) array analysis and TaqMan microRNA assays identified miR-503 and miR-222-5p as potential regulators of MSC differentiation into SMCs at early time points (Gu, et al., 2018).

In summary, these data prove the potential of MSC differentiation to ECs and SMCs, which are the two major cell types participating in neovascularization.

Tissue-engineered vascular graft architecture

TEVGs composed of muscle fibers in the outer layer and endothelial-like cells in the inner layer have been assembled with the most similarity to normal vessels in various papers using MSCs. A reason for using scaffold is providing a tubular surface for cell seeding. In these studies, after 6–8 weeks of MSC seeding, scaffolds were degraded. ECs suspended in the medium were then injected into the lumen to achieve the endothelial layer (Jung, et al., 2015, Zhou, et al., 2016). A summary of a TEVG architecture is shown in Fig. 3 by highlighting the most important factors in the differentiation process.

Conclusion

Vascular diseases can be life-threatening situations if they are not treated on time. In most cases, patients need graft

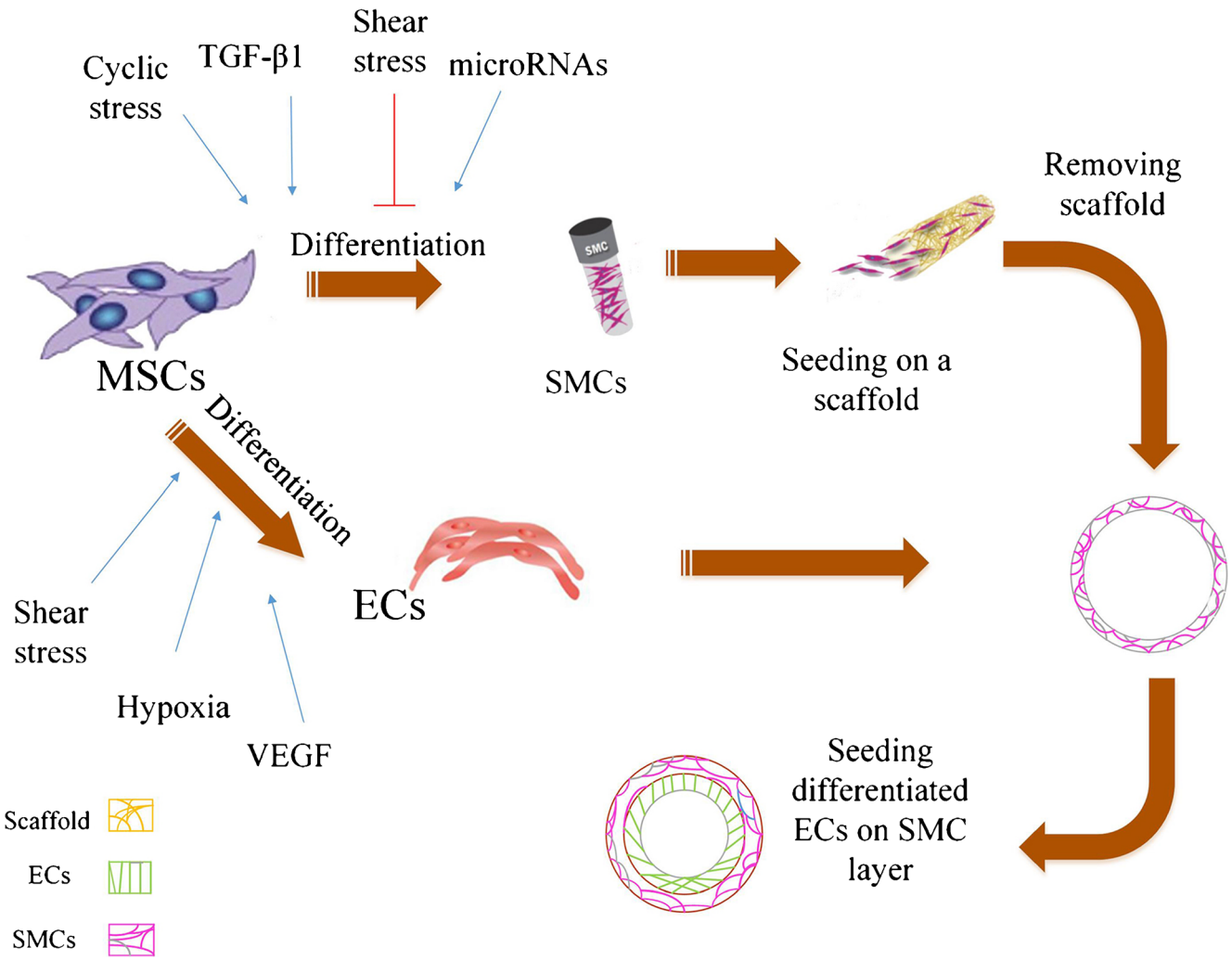

Fig. 3 Tissue-engineered blood vessel architecture illustrating the effects of different factors on every step of differentiation. MSCs mesenchymal stem cells, VEGF vascular endothelial growth factor, TGF-β1 transforming growth factor-β1, ECs endothelial cells, SMCs smooth muscle cells

implantation, while autografting suffers from the lack of suitable sources, in allografts we face the problem of immunogenic response. In this regard, an ideal solution is to have an off-the-shelf vascular graft to be available at any time for any patient with the lowest immunogenic response. To achieve this goal, it is necessary to use various approaches for making TEVGs that fulfill the basic requirements for a vessel graft. These requirements include low thrombogenicity and good mechanical strength which are accomplished by ECs and SMCs in native vessels, respectively. Thus, for making TEVGs, ECs and SMCs are the two most essential cell types.

Among all sources of cells, which are eligible for TEVGs, the most widely studied cells are mesenchymal stem cells (MSCs) and bone marrow mononuclear cells (BM-MNCs). There is not an original study comparing MSCs and BM-MNCs specifically in vascular engineering, but the immunogenic response of BM-MNCs is a non-negligible disadvantage in allografting. MSCs can be used for making allograft off-the-shelf TEVGs to be available at any time and with no immunogenic responses. Further studies are required to elucidate the long-term outcome of both mentioned cell types in clinical trials.

Taken together, this review demonstrates the potential of MSCs in making functional blood vessels for clinical trial studies with the hope of using this new therapeutic method in clinics with great success.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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