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From Endothelial Progenitor Cells to Tissue Engineering: How Far have we Come?

Barbara Salingova, Martina Madarasova, Stanislav Stejskal, Lenka Tesarova, Pavel Simara and Irena Koutna*

Centre for Biomedical Image Analysis, Faculty of Informatics, Masaryk University, 60200 Brno; Czech Republic

Abstract

Cardiovascular disease has become the leading cause of death in high income countries worldwide and the available treatment is not able to provide a complete recovery. Tissue engineering offers a possibility to construct autologous vein replacements for surgery. In this review we summarize approaches leading to artificial vascular graft construction. We discuss biomaterials currently in use, various drug delivery systems and the most appropriate cell cultures for vein engineering. Despite the progress in biomaterials and drug delivery systems, generating a suitable tissue microenvironment and selection of the appropriate cell population for graft seeding remains a major challenge. Here we focus on endothelial progenitor stem cells as the most suitable cell type for vascular graft construction. We discuss its sources, isolation techniques and differentiation procedures.

Keywords: EPC; *In vitro* vascularization; Small-diameter vessels

Introduction

Cardiovascular disease has become one of the most significant civilization health problems in the population of high income countries [1]. Modern medicine focuses on symptom treatment that is financially demanding and does not offer a permanent solution. In contrast tissue engineering and regenerative medicine offer a way to treat the underlined problem and achieve complete recovery [2-4]. New approaches in artificial vessel formation could significantly affect the therapy of ischemic injury, treatment of cardiovascular diseases and tissue engineering research. Tissue engineering is dependent on the ability to supply the tissue with nutrients and being able to dispose of the waste products. Vascularization is therefore an essential process in construction of any functional organ. In this context endothelial differentiation is becoming more and more attractive issue.

Human veins consist of multiple layers, each responsible for multiple functions within this complex system. The inner layer of endothelial cells forms a dynamic physiological barrier between circulating blood and the surrounding tissue. It protects the inner surface of the vein and regulates multiple physiological processes involving vessel repair, transport, coagulation and immune response [5]. It was believed that after embryonic development the repair and formation of new vessels occurred mostly through angiogenesis [5,6]. Angiogenesis is a process where postnatal vessel formation is perpetuated strictly by proliferation and migration of the neighbouring endothelial cells. However, this dogma was challenged when Asahara presented a new concept of postnatal vessel formation; postnatal vasculogenesis [7,8]. He isolated a bone marrow cell population that contributed to new endothelial formation and named them Endothelial Progenitor Cells (EPCs). This discovery changed the traditional understanding of vessel formation and proved that endothelial progenitors present in bone marrow do participate in vessel repair, and are able to form new vessels *in vivo* through process similar to embryonic vasculogenesis.

Multipotent stem/progenitor cells exist in nearly every organ of the human body [9,10]. They possess high proliferation activity and the ability to produce differentiated cell population in order to restore tissue homoeostasis. For example bone marrow is a source of various progenitor/stem cells including Hematopoietic Stem Cells (HSCs), Mesenchymal Stem Cells (MSCs) and EPCs [11,12]. These cells are isolated from bone marrow as a mixed cell population obscuring their origin and identity [13-16].

The EPCs play a major role in neovascularization [17,18]. The delivery of EPCs by injection or bioengineered vascular grafts resulted in enhanced angiogenesis in models of ischemia or infarction [19-21]. Despite the unresolved issues concerning the origin and differentiation mechanism of EPCs, their clinical application has encountered significant success in tissue engineering of large-diameter vessels, therapy of ischemic limb, and aneurysm and pulmonary arterial hypertension [22-26]. EPCs have also been investigated as a potential biomarker primarily for cardiovascular, but also several other diseases [27,28].

Origin of EPCs

EPCs are present all over the human body including in bone marrow, cord blood, spleen, the liver, intestinal and vessel walls, and blood stream circulation. They also show stemness and are able to differentiate into endothelial cells [29,30]. However, these properties were not shown to correspond with a unique surface expression pattern or easily detectable function [31,32]. The EPCs are isolated from bone marrow as a mixed cell population along with other cell populations with stem cell characteristics. Many of the surface characteristics are shared among various hematopoietic and endothelial precursor cell populations in different stages of differentiation, which obscures the origin and identity of EPCs. Furthermore, considering the plasticity of the stem cell phenotype, one or another particular marker cannot possibly define a distinct progenitor cell population. Table 1 offers an overview of various populations that produce EPCs and their

***Corresponding author:** Irena Koutna, Centre for Biomedical Image Analysis,FI, Masaryk University, Botanická 68a, 60200 Brno, Czech Republic, Tel: 420549493969; Fax: 420549498360; E-mail: qkoutna@fi.muni.cz

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surface markers used for isolation [8,32-46]. According to their growth patterns, we can distinguish early and late outgrowth EPCs in the *in vitro* cell culture. All of the mentioned factors account for both the lack of standardized criteria and cell surface markers used for characterization and isolation [47].

Mobilization of EPCs

One of the major disputed issues in EPC research is the incidence of EPCs in various tissues [29,31]. These cells are generally isolated from three major sources – umbilical blood, bone marrow and circulating blood [33,48,49]. Although several authors reported the isolation of CD34+ cells from peripheral blood, the cell population is too small for any major applications [41,50]. Tissue engineering approaches used mixed populations of endothelial and mesodermal cells for their applications. However several studies require relatively large numbers of EPCs. Mobilization of EPCs into peripheral blood is a relatively non-invasive procedure that provides the required quantity of EPCs [48].

In physiological conditions, the EPCs are largely restricted to bone marrow. EPCs incidence in peripheral blood remains low and relates to the state of the vascular system and lifestyle. Factors able to influence the EPC count include smoking, obesity and exercise [51-54]. Endogenous mobilization of bone marrow EPCs is a consequence of several pathological processes including ischemic injury, tissue trauma, wound healing, or tumor growth [55,56]. Induced mobilization of bone marrow stem cells into the blood stream increases EPC counts in peripheral blood and is a desired effect prior to isolation. Table 2 summarizes various endo and exogenous factors inducing mobilization of EPCs [57-71].

Bone marrow stem cell mobilization into peripheral blood is dependent on the local microenvironment consisting of fibroblasts, osteoblasts and endothelial cells. Mobilization occurs after the concentration of cytokines in blood exceeds the levels in bone marrow. They activate endothelial nitric oxide synthase and nitric oxide production, which leads to activation of metalloproteinases (MMPs) [55,72]. MMPs have the ability to release EPCs from bone marrow into peripheral blood [65,73].

Detection of EPCs

In several pathological situations EPCs can be used as a potent biomarker for determination of the cardiovascular condition of the patient [28,74]. Clinical studies focused on the evaluation of disease conditions including cardiomyopathy, ischemia, stroke, coronary artery disease and diabetes on the mobilization and function of EPCs [75-80]. The EPC-based therapy approaches rely on the extent of incorporation of the *in situ* mobilized cells. However, this process shows a high variability of 1-50%, which can be attributed to the patients genetic variation but also to the lack of standardization in the methodology. Modern isolation procedures make the process more effective and less time-consuming; however diversify the methodology even further [81-83]. Standard techniques for determination of the EPC count include isolation and cultivation, flow cytometry and Stromal cell-Derived Factor 1 (SDF-1) assay. Modern isolation procedures make the isolation and cultivation more effective and less time consuming, however that makes the methodology even more diverse [81,82]. The standardization of detection and cultivation procedures is therefore essential.

Origin	Precursor cell population	Surface characteristics	*In vitro* cell culture	References
Bone marrow	Post-natal hemangioblast	CD14+	Early outgrowth EPCs	[8,42]
	Myelo/monocytic progenitors	CD34+/VECFR-2+/CD133+	Late outgrowth EPCs	[8,33,35]
Mobilized peripheral blood	Post-natal hemangioblast	CD14+	Early outgrowth EPCs	[32,34,41]
	Myelo/monocytic progenitors	CD34+/VECFR-2+/CD133+	Late outgrowth EPCs	[32,34]
Adipose tissue	Adipose-derived stem cells	CD34+/CD146+	Early outgrowth EPCs	[36,37,38]
		CD34+/CD31+/CD133+	Late outgrowth EPCs	[44-46]
Umbilical cord blood	HSCs/MSCs/EPCs	CD34+/CD133+	Late outgrowth EPCs	[43,34]
		CD14+/CD133-	Early outgrowth EPCs	[43,34]
Blood vessel wall	EPCs/HSCs	CD34+/CD31-	Early outgrowth EPCs	[39,40]

Table 1: Endothelial Progenitor Cell (EPCs) populations, their sources for isolation, surface characteristic and cell populations obtained by *in vitro* cultivation.

Exogenous mobilization factors:		**References**
Cytokines	Granulocyte colony-stimulating factor (G-CSF)	[57]
	Granulocyte-macrophage colony-stimulating factor (GM-CSF)	[58]
Statins	Rosuvastatin	[59]
	Simvastatin	[60]
Growth factors	Vascular endothelial growth factor (VEGF)	[61,62]
	Basic fibroblast growth factor (bFGF)	[63]
Pharmacological agents	CXCR4 antagonist	[71]
Endogenous mobilization factors:		**References**
Growth factors	bFGF	[61,62]
	VEGF	[63]
	Erythropoietin	[64]
Statins		[67,69]
Chemokines	SDF-1	[65]
Cytokines	G-CSF (mobilizes CD34+ cells)	[57]
	GM-CSF (mobilizes EPCs)	[58]
Hormones	Parathyroid hormone	[66]

Table 2: Exogenous and endogenous mobilization factors (Exogenous factors are used for pharmacological induction of mobilization. Endogenous are naturally secreted in human body as a result of pathological conditions.)

Three major factors complicate the detection of EPCs (1) the heterogeneity of the EPCs (2) low incidence of CD34+/VEGFR-2 in peripheral blood (3) heterogeneity of the used techniques. The EPCs phenotype is shared among various cell types present in bone marrow or peripheral blood [84]. Therefore using 2-3 surface antigens for identification of a cell population with a complex function is a simplistic concept at best. Low incidence of CD34+, VEGFR-2+ cells in peripheral blood also complicates the analysis of the EPC count. They represent only 0,002% or 0,02% of total mononuclear cells isolated from peripheral blood or mobilized peripheral blood respectively [41,50]. Evaluation of these extremely rare events presents a problem and can lead to false positive results [31]. Finally, the last of the complicating factors is the heterogeneity of the techniques used for EPC quantification. To determine the EPCs incidence, flow cytometry and cultivation methods are commonly used. EPC cultivation methods do not take into account the fact that the final number of colonies obtained after the process does not correspond to the quantity of initially plated EPCs [31,85]. It is dependent on a complex set of processes involving adhesion, proliferation and differentiation of original cell. This heterogeneity complicates the comparison of the obtained data and results in misleading conclusions.

The quickest and most efficient method for determination the EPC count is detection by flow cytometry after marking. The greatest advantage is the parallel detection of endothelial and stem cell associated markers and the possibility to use analyzed cells for further cultivation. To define the phenotype of EPCs at least two markers should be used– a stemness marker to account for the stem cell potential as well as an endothelial marker to identify the endothelial characteristics of the progenitor populations. Most commonly used markers are CD34, CD133, VEGFR-2 [86,87].

An alternative method to determine the EPC count is an indirect quantification using Stromal cell-Derived Factor (SDF-1). It is an inducer of endothelial progenitor cell migration from the bone marrow. The method is based on the inverse correlation of SDF-1 and VEGF levels with EPC incidence. This method could potentially eliminate the inaccuracies caused by isolation, preparation and techniques of detection. It could therefore create a standardized parameter that would be comparable among different studies [88]. However the correlation of SDF-1 level and EPC count is a complex process involving unknown mechanisms that must be further studied before clinical application.

Isolation and Cultivation of EPCs

In vitro cultivation of EPCs provides two distinct cell populations [34]. They have been designated as early and late outgrowth EPCs with their distinct growth patterns and the ability to secrete angiogenic factors [32,43]. Although they have distinct origins and show functional differences *in vitro*, both were shown to contribute to *in vivo* neovascularization in several disease models. Mechanisms of action differ between cell populations and have not yet been precisely described [89-92].

The cultivation on fibronectine coated dishes with pre-plating yields early outgrowth endothelial cell population (eEPCs) [28]. Pre-plating is a procedure designed to avoid the contamination with early-adherent cells of mesodermal origin. The colonies start to appear after 4-7 days after re-plating and their numbers peek at 2-3 weeks. They can be maintained up to 4 weeks *in vitro*. They show a spindle-shaped phenotype and the expression surface markers CD14 and CD45 suggests hematopoietic origin. eEPCs do not incorporate into vessel walls. However are able to secrete multiple angiogenic, antiangiogenic and neuroregulatory cytokines and stimulate the process of endothelial formation. Therefore recent studies linked this cell population to primitive hematopoietic cells composed of monocytes and T-cells [93]. Some authors consider the eEPCs a manifestation of the multiple differentiation potential of monocyte/macrophage cell population, which allows them to assume an endothelial-like phenotype under appropriate cultivation conditions [94,95].

On the basis of eEPC cultivation a commercial assay has been developed by Hill and colleagues for the determination of cardiovascular risk [28,68,96]. Colonies begin to appear three days after re-plating. Positive eEPC colonies are characterized by specific morphology – round-shaped cells in the core and elongated cells on the periphery. These cells are also characterized by the expression of von Willenbrand factor, VEGFR-2 and CD31. Even though the derived cells do not incorporate into vasculature, this method showed correlation between the frequency of colony formation and cardiovascular risk. Low levels of EPCs in peripheral blood are considered a biomarker for cumulative cardiovascular risk. Easy execution and the ability to accurately characterize endothelial function and predict cardiovascular risk makes the eEPC assay a potent biomarker [97,98].

The second endothelial cell population, designated as late outgrowth cells, appeared after 2-3 weeks of cultivation and was able to be maintained in culture up to 12 weeks [24,34,99]. They showed an endothelial like phenotype, cobbelstone shape and apicobasal polarity. They expressed a complete endothelial phenotype, CD146, CD105 and lacked CD14 surface marker [100]. They have the ability to incorporate into cell walls and form junction-like cell-cell contacts as well as to form capillary tubes *in vitro* [32,101,102]. Therefore, these cells are considered true endothelial precursors and widely used for tissue engineering.

Blood Vessel Engineering

A promising application of EPC research is the utilization for vascular tissue engineering. Several strategies of vessel construction are nowadays in clinical trials. Even though large vessel transplants achieved encouraging results, clinical trials for small-diameter vessel replacements have encountered only limited success [23,103-106]. The tissue engineering triad consists of (1) scaffold with appropriate mechanical and biological properties (2) time-dependent angiogenenic stimulation (3) cells seeded in vitro or mobilized and guided to the injury site *in vivo*. Figure 1 explains the mechanism of *in vitro* engineering of vascular graft.

Scaffolds for tissue engineering must possess the three basic attributes: biodegradability, non-immunogenicity and must structurally substitute the function of the replaced tissue until the cell reconstitution is completed. Up to date several attempts aimed to construct veins and arteries suitable for application in transplantation medicine. First study dates to 1970, when Herring and co-workers seeded EC on polytetrafluoroethylene scaffolds [107-109]. However the used EP isolation method (mechanic scraping of the arterial endothelium) caused high impurity of the seeding material. More successful was the attempt of Weinberg and Bell in 1986 [110]. They constructed a tubular structure formed by collagen, bovine smooth muscle cells and non-degradable artificial material. The lumen was seeded with vascular fibroblasts and EC cells. The graft closely resembled native blood vessels, however did not possess the ability to withstand physiologic pressure bursts.Further research led to improvements in the biomaterials for

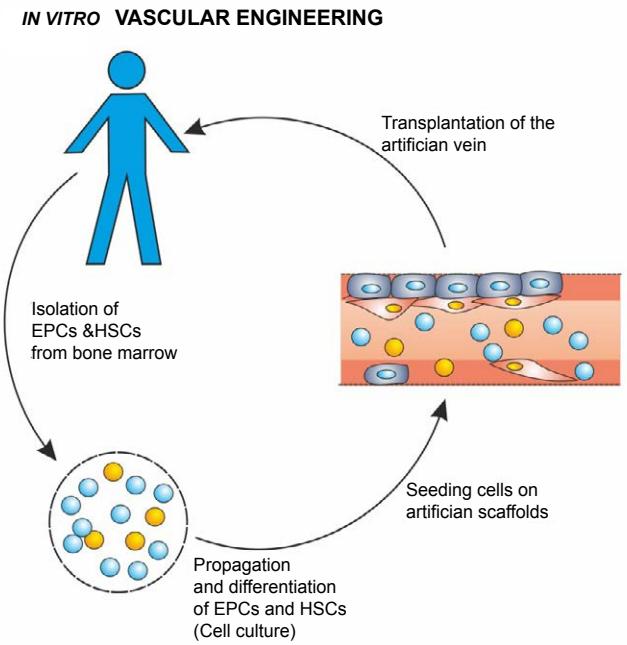

Figure 1: *In vitro*vascular engineering. EPC are isolated from patients mobilized peripheral blood and cultivated *in vitro*. Bioengineered scaffolds are seeded with EPCs (or co-cultures of EPCs) and cultivated in bioreactors in cotrolled conditions. Bioengineered graft is transplanted back to the patient.

scaffold construction and modification by extracellular matrix coating to achieve better cell adhesion properties [111]. Today the vascular design of the constructed vein is mechanically sound and satisfactory for clinical application. The blood vessels are able to withstand enormous pressures (above 2000mmHg) while retaining their contractible quality [112]. Materials for vascular replacements can be also modified to possess additional qualities to provide the ideal microenvironment for processes connected with vessel repair and for all intents and purposes to resemble the native tissue [113].

Currently, two major approaches are utilized in development of scaffolds for tissue engineering – the use of synthetic materials and organic tissues (decellularised human or animal blood vessels) [114-116]. The most commonly used polymers for construction of biopolymere scaffolds include Polycolicacid (PGA), Polylacticacid (PLA), Polycaprolactone (PCL) and Polyurethane (PU) [117-120]. They differ in their basic characteristics including biodegradability, elasticity and strength. In scaffold construction the ratio of the individual polymer components can be modulated to insure the desired properties and accommodate specific requirements of the transplantation site [121]. The most widely used polymere in preclinical studies is PGA. Artificial polymere scaffolds have hydrophobic surfaces and are therefore further modified with PEG, heparin or albumin to increase hemocompatibility [122].

Engineering of large-diameter vessels successfully utilized biodegradable scaffolds. The bioengineered graft showed long-term patency in mid- and long-term studies [103,123]. The composite polymer consisted of a tube composed of 50:50 ratio of PCL and PLA copolymer and a PGA woven fabric. The scaffold was seeded with autologous bone-derived cells. Twenty-five grafts were implanted into patients born with single ventricle cardiac anomalies [103]. A follow up study of long-term patency (7 years after implantation) showed promising results, when the implanted conduits were functional and none of the patients required additional graft replacement. 40% of the patients also did not require any medication related to their heart condition. However, 16% of the patients showed graft stenosis that was successfully treated. Although this pioneer study showed promising results, the mechanisms that lead to failure in small-diameter vascular grafts are still not understood.

In 1998 L'Heureux et al. [124] presented an alternative method of scaffold engineering – self-assembly [124-127]. The vascular graft was constructed without the use of bio-polymere material. This method takes advantage of the natural ability of mesenchymal cells to secrete native ECM. Mesenchymal cells are grown in over confluence producing self-assembled tissue sheets. They are further processed *in vitro* using a mandrel to form a tubular structure. A prolonged incubation period ensures the circumferential cell arrangement and large amount production of extracellular matrix [23]. These conduits are able to withstand high pressures and are currently under investigation for hemodialysis access grafts in human patients [128-130]. This approach has been successfully used in clinical trials for patients that do not need immediate bypass treatment.

A similar method was used in 2011 by Dahl et al. [131] in the construction of a human vascular graft using SMCs. The decellularized grafts were implanted into baboons [131]. The engineered constructs maintained patency for up to six months. This successful *in vivo* study was followed by clinical trials in Europe and USA in 2012 and 2013 respectively and is currently in progress [132]. Two major advantages of this approach include (1) acellular human-based grafts do not cause a significant immune response in nonhuman hosts (2) small-diameter vascular grafts show low rates of thrombosis [133]. This method is also currently being investigated for application in the vascularization of ischemic myocardium [134]. Its considerable limitation however lies in donor variability, the ability of the donor SMCs to form ECM *in vitro*.

Even though various tissue engineering approaches noted promising results in reconstruction of large vessels, they show discouraging performance in small-diameter application [110,135-137]. The main reason for these shortcomings is caused by increased thrombocity due to the absence of functional endothelium and the development of initial hyperplasia. Especially in low flow situations, small-diameter veins demonstrate low patency [138-141]. Although multiple efforts are aimed towards the development of new material substitutes and surface modification techniques, they are still not comparable with the performance of native tissues [142-144]. Table 3 contains an overview of pre-clinical studies in vascular engineering in the past years [70,103,118,131,145-147].

Angiogenesis *In vitro*

One of the major challenges of tissue engineering lies in the establishment of an environment that closely resembles *in vivo* conditions. These conditions can either be simulated artificially, where the angiogenic factors, or masterswitch activators are a part of a biodegradable scaffold, or the lack of growth factors can be compensated for by co-cultures [148,149].

The development of recombinant angiogenic and vasculogenic growth factors initiated research into its utilization for bioengineering. A number of growth factors have been tested in clinical trials including VEGF, PDGF, FGF and HGF (hepatic growth factor) [150-153]. Phase I trials reported promising results [154,155]. However, the results obtained in phase II did not demonstrate expected benefit to patients

[156]. These disappointing clinical results could be attributed to the short lived effect or instability of the injected medicament as well as to the multiple issues related to viral infection procedures.

Recombinant proteins or direct administration of medicament provide burst-release dosing. In contrast, bioengineered transplants require a sustained and controlled release of growth factors to facilitate a prolonged treatment. Table 4 shows a list of angiogenic stimulants and their role in vascularization in chronological order [72,157-163]. In contrast to the burst-release dosing, microparticle release mechanisms allow for the time-dependent release of the angiogeneic stimulation. They are constructed from biodegradable materials for example poly (lactic-co-glycolic acid) (PLGA) or acetylated dextran(AcDex) [20,164]. Several different combinations of angiogenic signaling molecule sand delivery systems were studied [165-169]. These studies showed encouraging results, however were not able to achieve the full restoration of function due to the complexity of the healing process.

Perspective 'release-on-demand' platforms represent yet another alternative approach to the delivery systems [170]. They use the principles of enzyme-mediated growth factor release. It is able to provide a time- and location-restricted release of the growth factors. It was shown that regulated delivery of angiogenic and blood vessel maturating factors was able to form functionally mature vessels composed of ECs and smooth muscle cells (SMCs) *in vivo* [170,171]. Even though it is a complicated system and our knowledge of wound healing physiology remains limited, several release systems have already been successfully established [172-176].

Research into "master switch" upstream activators such as HIF-1α (hypoxia inducible transcription factor 1 α) that induces pro-vascular signaling cascade represents a new research direction in the growth factor delivery field [3,5,177]. HIF-1 is a heterodimeric transcription factor composed of two subunits, HIF-1α and HIF-1β that are constitutively expressed in most cell types [90,178,179]. Under standard conditions, HIF-1α protein is rapidly degraded by ubiquitin–proteasome system. Hypoxic environment on the other hand stabilizes HIF-1α and consecutively activates the transcription of multiple pro-angiogenic proteins such as VEGF, SDF-1 and MCP-1, angiopoietins and erythropoietin, which recruit both CD14+ EPCs and CD34+ EPCs from the bone marrow into the circulation, towards the site of hypoxia [25,64,180-182]. In contrast with the strategy that aims to carefully bioengineere an environment with pro-vascularization properties, this approach has the potential to induce native regeneration process *in vivo*.

The Co-cultures of EPCs with Supportive Cells

In spite of several successes, most studies have demonstrated that the dynamic multistep cascade of angiogenic stimulation in the cellular niche required for vessel regeneration cannot be achieved by addition of one, or multiple angiogenic factors [183-185]. Co-cultures offer a perspective new tool in tissue engineering that has the potential to lead to qualitative and quantitative progress in seeding of the artificial scaffolds and construction of vascular grafts [149,186,187]. As was recently shown, a co-cultivation of different cellular subtypes is able to induce a microenvironment that mimics the cellular niche during the vascularization process. The angiogenic potential of several hematopoietic, mesenchymal and endothelial cell populations has been studied in the context of vessel repair. This mechanism has the potential to regulate vessel repair by paracrine signaling in a coordinated sequence of signaling events. Different cell populations effect distinct phases of vessel regeneration and therefore a diverse population for vascularization is imperative.

The co-culture of early- and late-outgrowth EPCs demonstrated the importance of angiogenic stimulation during vascularization process. Both cell populations secrete multiple cytokines after proangiogenic stimulation, including HGF, insulin-like growth factor 1 (IGF1), FGF and VEGF [188-190]. Their interaction synergistically increases the secretion of pro-angiogenic mediators and supports the differentiation process. Co-cultivation of CD14+ and CD34+ cells isolated from peripheral blood was able to create an endothelial layer on 3D scaffold more effectively than CD34+ cells alone [188,190,191]. Although this mechanism increases the endothelial differentiation *in vivo* as well as *in vitro*, the effectiveness of the system remains low due to the immature structure of the cultured EC networks. Despite this fact CD14+ or eEPCs are an important contributing factor in the process of vascular regeneration [192].

Recently mesenchymal and endothelial cell co-cultures have been studied to describe the influence of paracrine signaling between cell populations throughout the vasculogenic process. It was shown, that in endothelial-mesechymal co-cultures. Mesenchymal stem cells (MSCs) acquire pericyte phenotype and promote generation of vasculatory network [193-195]. Examination of the MSCs isolated from four

	Biomaterials	Cells	Long-term pat.	Model	Dimensions	CT	References
2006	Self-assembly	ECs	5-8 weeks	maccaques	large-diameter	CT	[71]
2010	PGA/PCLL	BM-MNCs	5,8 years	clinical t.	large-diameter	CT	[103,145]
2010	PLA, fibrin	SMCs, ECs, fibroblasts	6 months	sheep	small-diameter	-	[118]
2011	Decellularised art.	SMC and ECs	4 months	sheep	small-diameter	-	[146]
2011	Polyester/collagen	SMCs and ECs	8 weeks	pig	small-diameter	-	[147]
2011	Self-assembly/PGA	ECs	5-8 weeks	baboons	small-diameter	CT	[131]

Table 3: Biomaterials, cell cultures and research models used for preclinical studies in recent years. (Abbreviations: CT - currently ongoing clinical trials, PGA – polyglycolic acid, PCLL - a copolymer of polylactic acid and caprolactone, PLA – polylactic acid.)

Growth/signaling f.	Molecular type	Function	References
VEGF	Cytokine	Initiator of vessel remodeling and repair	[72,157,158]
bFGF	Heparin-binding protein	Initiates proliferation of EC and SMCs	[72,159]
HGF	Mitogen	Stimulates growth of ECs	[160]
PDGF	Mitogen	Recruits SMCs, promotes maturation of the blood vessel	[72,161,162]
Angiopoietin-1	Growth factor	Promotes blood vessel maturation, regulates homeostasis	[163]

Table 4: Angiogenic growth factors involved in vasculogenesis with a brief description of their essential roles in the process. The signaling factors are arranged in chronological order according to their function.

distinct tissues demonstrated that this ability is shared among MSCs. In the native tissues pericytes reside in close proximity to ECs. They encompass blood microvessels, and coproduce a basement membrane with ECs demonstrating that pericyte-endothelial interaction plays a key role in basement membrane formation, remodeling and maintenance [196-199]. Furthermore, pericytes have been shown to be critical regulators of vascular development, maturation, remodeling and maintenance of homeostasis by production of angiogenic stimulants including transforming growth factor β (TGFβ), PDGF and angiopoietin-1 [200-203]. Moreover several models ofpericyte-endothelial co-cultures showed best results in direct cell-cell contact co-cultures [195,204]. It was shown that pericytes are also present around an engineered blood vessel and are essential for *de novo*vessel formation [197,205].

A 3D microvascular model of co-culture of endothelial cells and various other cell populations including lung fibroblasts, cancer cells and pericytes, investigated the effect of cell populations during critical phases of vascularization. Interestingly it showed that lung fibroblast-produced chemotactic gradient was required for both vasculogenesis and angiogenesis [206]. Without fibroblast co-culture Human Umbilical Vein Endothelial Cells (HUVECs) were not able to form intra-connected networks. Later in the process MSCs co-culture created a well intra-connected network. However, in accordance with *in vivo* studies this network was non-perfusable which suggests an essential unknown paracrine variable in the process.

Even though, to date, a perfusable 3D vascular system has not been created, mounting evidence shows that the synergistic effect of paracrine signaling of multiple cell populations has the potential to establish a working model. As we indicated stem cell populations used for vascularization show significant plasticity, and can undergo the differentiation process or Trans-differentiate depending on the microenvironment and presence of other cells.

Conclusion

Several experimental avenues have been taken for the engineering of functional blood vessels *in vivo*. Currently, many of these approaches are in the phase of clinical trials. Some have encountered encouraging results, mostly in engineering of large-diameter vascular grafts. However, modern tissue engineering is still not able to restore the function of small diameter arteries. Nonetheless, all of these approaches have solidly established proof of the principle that it is possible to engineer a transplantable blood vessel, functional and durable *in vivo*. Yet none of the techniques has received any widespread application.

In this review, we summarized the tissue engineering approaches that are currently under investigation. We have focused mainly on the various cell populations involved in the process of vascular reconstitution. We have documented all the known methodologies for the detection and isolation of distinct EPC populations and gathered information about their interaction with other cell types in co-cultures and in *in vitro*vessel engineering conditions. It has been shown that vascular graft constructs do not require a pure EPC culture. Co-cultures possess the advantage of reciprocal angiogenic stimulation and are able to more closely mimic the physiological conditions in the site of injury. The creation of an appropriate microenvironment for EPC differentiation and maturation is a priority for the construction of a vascular graft.

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