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Tissue engineered vascular grafts

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ABSTRACT

With the continuous increase in the prevalence of cardiovascular diseases and the limited efficiency of conventional treatments, including diet and lifestyle modifications, pharmaceutical administration, and surgical interventions, there is an equally increased need for vascular grafts for the replacement of damaged blood vessels. Currently, autologous grafts represent the gold standard. However, due to the limited availability, intensive work has been performed in the field of vascular tissue engineering. Although there are many possibilities for obtaining synthetic vascular grafts, there is still no ideal solution for vascular replacements. In this paper, the main material categories and fabrication techniques are reviewed.

Keywords: *blood vessels, vascular grafts, vascular tissue engineering, decellularized matrix, blood vessel bioprinting, endothelial cells, cell seeding.*

1. INTRODUCTION

The cardiovascular system consists of a two-sided, four-chambered heart responsible for the directional movement of blood through the closed, endothelial cell-lined vessels. Additionally, there is a strong connection between the cardiovascular system and the proximate ends of the lymphatic system (Schultz and Bader, 2018). The main function of this complex system is the circulation of oxygen and nutrients to the cells, and carbon dioxide and metabolic byproducts from the cells. Moreover, it is also responsible for maintaining the immune system of the body, stabilizing the precise temperature and pH, and homeostasis (Padsalgikar, 2017).

Throughout the vascular system, four different segments can be identified. Specifically, it consists of the arterial segment, which can be further categorized into elastic and muscular arteries, the venous segment, the lymphatic segment, which includes lymphatic vessels and lymphatic capillaries, and the microcirculation, constituted by arterioles, capillaries, and venules. The latter segment is interposed between the arterial and venous segments, and it represents the major exchange area between the circulating blood and the peripheral tissues (Berridge et al., 2018).

The formation of the normal vascular walls implicates a strictly regulated process of cell adhesion, proliferation, migration, and differentiation. As it is composed of various distinct cellular types and layers, the structure of the vessel is highly dynamic and versatile, involving distinct communication pathways between individual cells and between layers. The development of modern engineering, biological, and genetic approaches has led to paradigm-shifting insights into the pathogenesis of cardiovascular diseases (Mazurek et al., 2017). With an estimated 422.7 million cases of cardiovascular diseases in 2015, of which 17.92 million resulted in death, they are the worldwide leading cause of health issues and deaths (Roth et al., 2017). Triggered by abnormalities regarding the structure and function of the microvascular arteries and large arteries and veins, cardiovascular diseases progress through biological processes leading to fatal events, such as myocardial infarction, stroke, heart failure, and other vascular morbid events (Cohn, 2018).

The most prevalent vascular diseases include atherosclerosis, vasculitis, aneurysms, and varicose veins. Affecting large arteries, such as the aorta, carotid, coronary, iliac, and cerebral arteries, atherosclerosis is an inflammatory and multifaceted disorder caused by the deposition of plaques formed through the accumulation of lipids and immune cells, such as macrophages, T and B lymphocytes, on the arterial wall (Abdolmaleki et al., 2018). Furthermore, vasculitis is the cardiovascular disease causing the inflammation of any type of blood vessels, including arteries, veins, and capillaries (Tehrani and Hariman, 2017). Characterized by a focal increase of at least 50% of the vascular lumen, aneurysms can occur in both arteries and veins and are associated with degenerative changes in the vascular connective tissue matrix, hypertension, and age (Carey and Sheppard, 2018, Sheppard, 2015).

Conventional treatments for vascular diseases commonly involve diet and lifestyle modifications, pharmaceutical administration, and surgical interventions. Although typical surgical procedures focus on angioplasty, stent insertion, or atherectomy, vascular grafts for the replacement or bypassing the damaged or obstructed vessels are often used as they are considered the optimal choice for many patients (Pashneh-Tala et al., 2015). Although autologous arteries and veins represent the gold standard for vascular grafting, there are several limitations associated with this approach, specifically the unsuitability (Kumar et al., 2011), limited availability, poor quality of the vessels, the morbidity at the donor site (Pashneh-Tala et al., 2015), and vascular grafts infections (Settembrini and Settembrini, 2017).

However, there are also specific limitations associated with synthetic vascular grafts, namely infection, thrombosis, stenosis, calcification, anticoagulation therapy necessities, lack of durability, and inability to allow the regeneration of the native tissues (Miyachi et al., 2019). To address these concerns, novel strategies related to vascular tissue engineering have been developed. The purpose of these applications does not only focus on the fabrication of a vascular tube with properties similar to the native blood vessels, but also on the biomimicry of the process of extracellular matrix assembly after implantation. The expected results of the tissue engineered vascular grafts is the incorporation of the vessel in the vascular system by avoiding the immune response of the body to foreign materials (Benrashid et al., 2016).

The aim of this review is to present the requirements of these grafts related to the properties of the native blood vessels and the current and emerging strategies for vascular tissue engineering.

2. NATIVE BLOOD VESSELS

As previously implied, the vascular system consists of the macrovasculature, comprising blood vessels with diameters higher than 100 μm, and the microvasculature (Grant and Karsan, 2018). The wall of both arteries and veins is composed of three main layers, with individual structures specialized for specific functional demands (Figure 1) (Carlson, 2019, Oikonomou et al., 2018, Almeida, 2019). The inner layer, termed as the tunica intima, consists of the endothelium, a thin monolayer of endothelial cells which is the interface between the circulating blood and the vessel wall (Moncada, 2018), the basement membrane, a support for the endothelial layer containing extracellular matrix molecules, such as collagen, laminin, and fibronectin, and the elastic membrane, the connection between the intima and the middle layer. Additionally, veins exhibit valves with bicuspid structures, which are extensions of the intima for maintaining the unidirectional flow (Almeida, 2019). The middle layer, termed as the tunica media, is composed of smooth muscle cells intermingled with layers of connective tissue fibers. In highly elastic vessels, such as the aorta, it is rich in elastin, as it is necessary to store the kinetic energy powered by the heart ejection, while in veins, the muscular tunica media is considerably thinner (Almeida, 2019). The outer layer, the adventitia, primarily consists of collagen fibrils and a population of fibroblasts and mast cells. In large vessels, the adventitia also contains small blood vessels (vasa vasorum) and nerve endings (Carlson, 2019, Oikonomou et al., 2018). The capillaries, however, solely consist of a thin monolayer of endothelial cells which allows for a minimal barrier thickness and a large surface area for the process of passive diffusion (Egginton and Syeda, 2017).

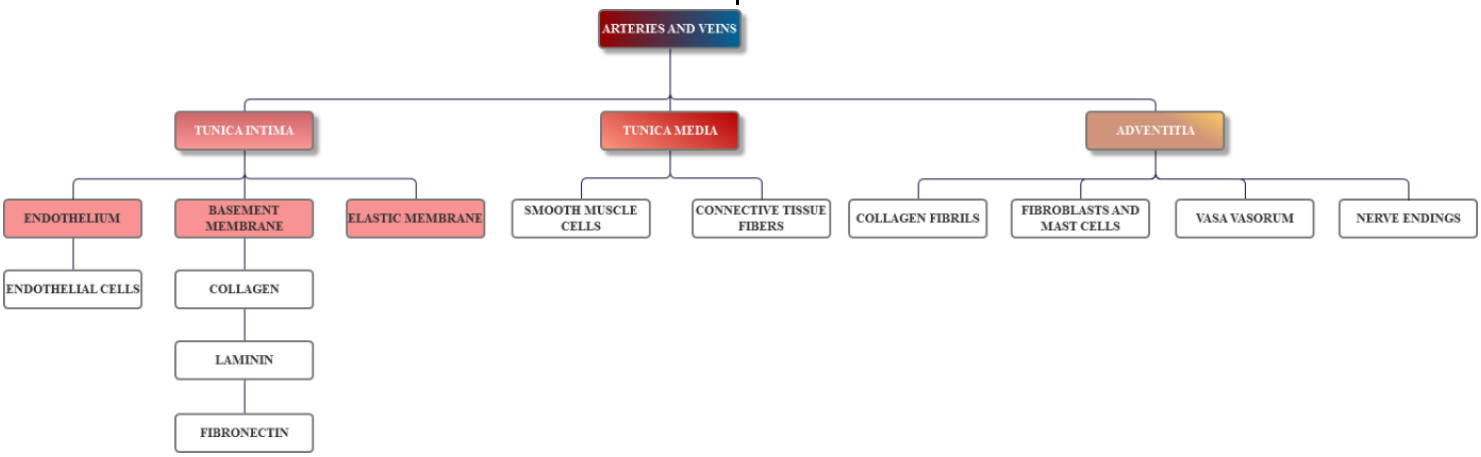

Figure 1. The main components of the arterial and venous wall

The formation of blood vessel involves two main processes. The process of vasculogenesis leads to the formation of the earliest vessels through the differentiation of mesodermal cells into endothelial precursor cells called angioblasts and the subsequent differentiation of angioblasts into endothelial cells that will coalesce and form the first tubular vessels. Recent work has proved that endothelial cells are genetically guided towards the specific formation of either arterial or venous vessels (Stratman et al., 2015). The second process, the angiogenesis, which occurs throughout the entire life, is mediated by blood circulating platelets where many angiogenesis-related proteins are stored in the alpha-granules. Platelets accumulate at the site, where they simultaneously form clots and release growth factors from the alpha-granules, initiating the blood vessel formation (Kareva, 2018).

Each segment of the circulating system is responsible for specific functions. Hence, the arterial system is responsible for the transportation of blood to tissues, the resistance against changes in blood pressure, and the regulation of blood flow; the venous system is responsible for the return of the blood to the heart and the vascular capacitance, and capillaries, for maintaining the vascular tone and metabolism (Grant and Karsan, 2018). Therefore, specific requirements must be fulfilled by each vessel in order to accomplish these functions.

The dimensions of human blood vessels are, on average, 4 mm diameter and 1 mm thickness for arteries and 5 mm diameter and 0.5 mm thickness for veins, with 60 μm for the intima and 360 μm for the tunica media (Li, 2018, Neufurth et al., 2015). However, these dimensions are not available throughout the entire circulatory system, as the diameter can reach 3.5 cm in the

ascending aorta (McComb et al., 2016), 2.5 cm in the inferior vena cava (Patil et al., 2016), and 3 μm in capillaries (Cortés-Sol et al., 2013).

With each heart ejection, there is a pulse wave created which travels throughout the arterial vasculature (Peter et al., 2018). The diameter of the arteries varies with the pulsating pressure to maintain a constant blood flow and to further propagate the pulse (Mohiaddin, 2019). Therefore, the characteristics of the arterial wall, such as elasticity, stiffness, and thickness, are key factors for the physiological condition of the cardiovascular system, causing severe diseases in the case of significant modifications (Mohiaddin, 2019, Peter et al., 2018). Moreover, the biomechanical properties of veins are equally important, characterized by active characteristics involving the contraction of smooth muscle cells under the action of a stimulus, and passive characteristics, associated with the elasticity and viscoelasticity of the wall under a transmural pressure (Li, 2018). The mechanism for pulse propagation involves the generation of a negative pressure gradient at the forefront, which will accelerate the blood, leading to a spatial gradient of flow rate with a higher flow rate entering than leaving a segment of the vessel. Consequently, through the conservation of mass, the vessel will expand, and the pulse will be propagated (Secomb, 2016). This phenomenon is a consequence of the vascular compliance, which represents the amount of distention for a given amount of pressure. Thus, the greater the change in volume for the given pressure change, the higher the compliance is. Furthermore, by dividing the compliance by the base volume of the vessel, the distensibility of a specific vessel can be determined. Since arteries are thicker and contain more muscular cells, the arterial compliance is lower than the venous compliance while the arterial pressure is considerably higher than in veins. Moreover, as veins are significantly more distensible, a high proportion of the circulating blood is located in the venous system (Kumar et al., 2019).

Burst pressure, another important mechanical property of blood vessels, is defined as the pressure which causes leakage from a seal or the rapid drop in pressure in a pressure/time curve. Common burst pressure tests are pass/fail tests, where passing is associated with the capacity of a seal to withstand a specific amount of pressure (Krane et al., 2011). Native arteries are characterized by burst pressures with values in the range of 0.22-0.5 mmHg (Castillo-Cruz et al., 2018).

Although the suture retention strength is not necessarily fundamental for native vessels, it is important to consider this characteristic in the context of vascular grafts. The suture retention strength, also known as the anastomotic strength, is defined as the "the force necessary to pull a suture from the prosthesis or cause the wall of the prosthesis to fail" or the highest force value reached during the pullout of the suture. Vascular grafts are often characterized in regard to their capacity to withstand a 2 N force (Pensalfini et al., 2018).

The above-mentioned characteristics and properties are summarized in Table 1 for two representative blood vessels.

Table 1. The values of the inner diameter, wall thickness, compliance, burst pressure, and suture retention strength for the human carotid artery and human saphenous veins

Blood vessel	Inner diameter [mm]	Wall thickness [mm]	Compliance [%/mmHg]	Burst pressure [mmHg]	Suture retention strength [g]	Reference
human carotid artery	7 (Pomella et al., 2017)	1 (Zhang et al., 2018)	5.4	0.45	200	(Johnson, 2015)
human saphenous vein	2.5 – 6.5 (Engelhorn et al., 2017)	0.3-0.6 (Labropoulos et al., 2017)	1.1	0.17-0.25	200	(Johnson, 2015, Neufurth et al., 2015)

3. STRATEGIES FOR VASCULAR TISSUE ENGINEERING

In the process of manufacturing vascular grafts, several requirements must be met in order to avoid grafting failure. Specifically, vascular grafts must be biocompatible and resistant to infections and possess suitable mechanical and vasoactive physiological properties, and they should be hermetical and resistant to thrombosis. Additionally, the fabrication process should allow for the production of sufficient amounts for clinical applications (Popryadukhin et al., 2017).

Vascular graft failure can occur in three different phases: in the first 30 days, caused by technical errors, such as poor anastomosis or inflow/outflow or a retained unlysed valve cusps, after 30 days up to 2 years, due to high thromboreactivity or intimal hyperplasia, and after 2 years, caused by dyslipidemia and the progression of atherosclerosis (Richa et al., 2014).

There are several strategies employed for the development of vascular grafts, namely autografting and allografting, polymeric vascular graft fabrication, and matrix decellularization. The introduction of these scaffolds into the body can be preceded by the process of cell seeding for a better acceptance of the graft.

3.1. Autografts and allografts

The gold standard for vascular grafting is represented by autologous arteries and veins. Autograft arteries such as the internal thoracic artery and the radial artery (Wenger and Giraud, 2018, Fukunishi et al., 2017), are associated with superior patency, with 10-year rates of 90% (Pashneh-Tala et al., 2015, Tara et al., 2014). However, due to the limited availability of arteries and the severe complications related to their removal, the most commonly used autologous vessel is the saphenous vein (Pashneh-Tala et al., 2015), with a 10-year patency rate of 50% (Tara et al., 2014).

The use of autografts is associated with several disadvantages of which the lack of natural grafts for patients who need multiple grafting is the most important (Wenger and Giraud, 2018). Autografting often results in failure after 10 years due to poor quality, size mismatches, and atherosclerosis (Fukunishi et al., 2017, Pashneh-Tala et al., 2015). Additionally, harvesting and preparing the autograft tissue require careful handling and the extraction often leads to donor site morbidity (Pashneh-Tala et al., 2015, Tara et al., 2014). To preserve the autograft, the extraction techniques should cause minimal trauma and the intraoperative

distention checking and the reperfusion timing should not affect the structure and function of the endothelium (Ben Ali et al., 2018).

Although they were the first widely used vessel grafts, their chronic rejection has reduced the clinical application of allografts. The consequences of the rejection process involve the thinning of the tunica media, the dislocation of the elastic lamellae, the progressive destruction of the smooth muscle cells, and the infiltration of inflammatory cells into the adventitia (Ha et al., 2016). Although cryopreserved allografts exhibit enhanced mechanical properties than fresh allografts, they are still limited by disruptions, aneurismal degenerations, and thrombosis (Minga Lowampa et al., 2016). Another key issue of allograft tissues is the risk of disease transmission, which requires additional disinfection and sterilization techniques (Moore et al., 2019).

3.2. Biomaterials for vascular tissue engineering

3.2.1. Synthetic non-degradable polymers

Non-degradable polymers, including polyethylene terephthalate (PET and Dacron), polytetrafluoroethylene (Gore-Tex), and expanded polytetrafluoroethylene (ePTFE) are the common choices for synthetic vascular grafting for vessels larger than 6 mm in diameter, such as the aortic, iliac, and common femoral arteries (Wenger and Giraud, 2018, Chang and Niklason, 2017, Love, 2017). These biomaterials exhibit several advantages, such as biocompatibility, low risk of thrombosis, tunable size and form, cost-effectiveness, and ease of surgical handling due to their adequate mechanical properties in terms of compliance and blood flow resistance (Wenger and Giraud, 2018). The manufacturing techniques involve knitting or weaving through which suitable pore sizes that allow for a certain radial blood permeation along with the axial perfusion can be achieved. Additionally, these constructs can be obtained through the kinking process, through which a corrugated structure more flexible than the multifilament wave is formed (Love, 2017).

Vessel replacement with synthetic prostheses might cause infections post-implantation and the recommended treatment involves the debridement of the infected tissue and the long-term administration of antibiotics (Aldridge et al., 2018). However, several modifications can be performed to reduce the infection rate by increasing the resistance against bacterial adhesion (Gharamti and Kanafani, 2018, Chang and Niklason, 2017). One strategy involves coating the synthetic graft with extracellular matrix and antibodies, which will promote the endothelialization by capturing the endothelial progenitor cells and supporting their differentiation into endothelial cells (Gharamti and Kanafani, 2018).

Synthetic polymers can also be used for small diameter vessel grafting. However, intima hyperplasia, thrombosis, and infection affect the long-term patency of these grafts. Due to the differences regarding the mechanical properties of native tissues and synthetic grafts, blood flow disturbances and wall shear stress will lead to endothelial injuries and, consequently, to vascular failure (Wenger and Giraud, 2018).

3.2.2. Synthetic biodegradable polymers

Another approach for vascular grafting is the use of biodegradable polymers for scaffold development. These polymers have been extensively studied as they have the capacity to degrade in a controllable manner, allowing for the endothelialization of the graft by the host's cells. As they gradually secrete the extracellular matrix, the graft will be replaced by the endogenous vessel (Liu et al., 2018). Most commonly used materials are polyglycolic acid, polylactic acid, poly(lactide-co-glycolic) acid, poly ε-caprolactone, polyurethanes, and poly(glycerol-sebacate) (Liu et al., 2018, Carrabba and Madeddu, 2018). Polyurethanes and poly(glycerol-sebacate) are bioresorbable polymers with remarkable properties in terms of biocompatibility, hemocompatibility, and low thromboreactivity, allowing for endothelial cell proliferation and elastin production (Carrabba and Madeddu, 2018). Although the mechanical properties and the degradation speed can be modulated by applying combinations of polymers (Liu et al., 2018), there is still need for improvements, since the burst pressure of these grafts is 0.19 mmHg (Carrabba and Madeddu, 2018). However, biodegradable polymers exhibit enhanced mechanical properties and high reproducibility compared to natural polymers. Among them, only polyglycolic acid, polylactic acid, poly ε-caprolactone, and poly(glycerol-sebacate) are approved by the Food and Drug Administration for human clinical use (Yalcin Enis and Gok Sadikoglu, 2018).

3.2.3. Natural polymers

Natural polymers have been studied as an alternative for the lack of bioactivity of synthetic vascular grafts. Therefore, extracellular matrix-derived proteins have gained great scientific research since they provide natural binding sites for cell adhesion, biomimicry, and biocompatibility. Among them, collagen, gelatin, elastin, and fibrin are the most commonly applied in vascular tissue engineering (Carrabba and Madeddu, 2018). Other natural polymers, including silk fibroin and chitosan, have also been used as materials for scaffold fabrication. Though, despite the outstanding biocompatibility and cell adhesion, mechanical properties are still limiting their application in vascular tissue engineering (Kabirian et al., 2018).

However, silk fibroin has been clinically applied as regenerated vascular tissues as a result of new knowledge regarding its processing. Thus, the properties of silk fibroin, such as mechanical strength, elasticity, and biodegradability, can be modulated (Abruzzo et al., 2014).

3.2.4. Decellularized matrices

Due to the poor patency rate of conventional synthetic grafts, novel strategies have been investigated to overcome their limitations. Vascular grafts obtained from the decellularization of native blood vessels has become an important field for vascular tissue engineering. Hence, the issues associated with donor vessel shortage and adverse immune responses can be overcome by using decellularized scaffolds obtained from allogenic or xenogenic sources. Moreover, these tissue scaffolds should be able to resist physiological blood pressure, as they possess similar structure and mechanical properties as native vessels (Simsa et al., 2018, Lin et al., 2018). Studies showed good endothelialization and smooth muscle cell migration in the media for venous grafts, and partial recellularization of the media and adventitia for arterial grafts (Porzionato et al., 2017).

Decellularized grafts available on the market are mostly of xenogenic source, derived from bovine vessels, and their clinical outcomes are not completely satisfactory due to their associated thromboreactivity, infections, and aneurysms. Decellularized vessels derived from human vessels, including umbilical artery and umbilical vein, and porcine vessels, including carotid artery, radial artery, saphenous artery, and iliac artery, are currently investigated for their potential in vascular tissue engineering (Lin et al., 2018).

The decellularization process involves the complete removal of cells and genetic material with the simultaneous maintenance of structural proteins (Gilpin and Yang, 2017). Therefore, decellularized grafts represent the extracellular matrix of the native blood vessels (Simsa et al., 2018). There are several methods available for decellularization, including chemical, physical, and their combinations, each offering advantages and disadvantages regarding the recreation of the blood vessels (Gilpin and Yang, 2017, Xu et al., 2017). The recellularization process using endothelial cells before or after the implantation has been related to a reduced risk of thrombosis, as the endothelium prevents blood clotting and formation of intimal hyperplasia and graft atherosclerosis (Simsa et al., 2018).

Furthermore, studies have proved that polymer coating of the decellularized scaffolds is an aid in improving the re-endothelialization, maintaining or enhancing the mechanical properties, and reducing the thrombogenesis. One example of such polymers is the poly(ethylmethacrylate-co-diethylaminoethylacrylate), which facilitated the adhesion of endothelial cells, while reducing the adhesion of platelets, induced the formation of capillary tubes, and increased the tensile strength and load of the graft (López-Ruiz et al., 2017).

3.3. Vascular tissue engineering techniques

3.3.1. Scaffold fabrication and cell seeding

The fabrication of vascular conducts is possible through a variety of methods, such as sheet rolling, through which a sheet of the material of choice containing or not cells is rolled over a mandrel to form a tubular structure, tubular molding, which implicates the injection and crosslinking of the material inside an annular mold, and direct scaffolding, through various techniques (Song et al., 2018). Most common techniques are electrospinning, molecular self-assembly, hydrogels, thermally induced phase separation, solvent casting-particulate leaching (Rychter et al., 2017), and freeze-drying (Carrabba and Madeddu, 2018).

The most promising technique for vascular scaffolds is electrospinning owing to the possibility of obtaining one-dimensional nanostructures and microstructures and controlling the morphology of the structure and the overall efficiency of the procedure (Rychter et al., 2017). Furthermore, it allows for the use of a wide range of materials, including non-degradable and biodegradable polymers, structural proteins, and their mixtures or copolymers (Yalcin Enis and Gok Sadikoglu, 2018).

Moreover, vascular grafts can be obtained by using combinations of the above-mentioned techniques and materials to enhance their performance. One example is the development of a vascular graft through electrospinning and freeze-drying that can mimic the characteristics of native coronary arteries. The fabrication involved the co-electrospinning of poly ε-caprolactone and gelatin solution containing heparin to form the inner layer. Subsequently, the gelatin hydrogel was freeze-dried to form the porous outer layer that could allow for the proliferation of smooth muscle cells. Results showed enhanced endothelial cell attachment and proliferation, reduced thrombosis, and improved mechanical properties compared to the individual layers of the scaffolds (Norouzi and Shamloo, 2019).

The strategies applied for reducing the risk of thrombosis involve the chemical treatment of the surface, limited by the short half-life of the anti-thrombotic moieties or the lack of endothelial selectivity, seeding anti-thrombogenic cells onto the surface, or their combination (La and Tranquillo, 2018). Comparative studies showed that acellular grafts present thicker intimal hyperplasia associated with reduced and disturbed blood flow, proving the potential of mesenchymal stem cells to reduce hyperplasia and enhance the healing process (Madhavan et al., 2018). There are several strategies to direct the differentiation of mesenchymal stem cells into endothelial phenotypes, such as chemical and biomechanical stimulation. The preferred source for this type of cells is the adipose-derived mesenchymal stem cells owing to the possibility to extract them from the autologous source in a sufficient amount for seeding a monolayer onto the luminal surface of the graft (La and Tranquillo, 2018).

3.3.2. Bioprinting

The emergence of 3D printing has led to the application of additive manufacturing for the fabrication of organoids and tissues (Maina Renee et al., 2018). Bioprinting vascular grafts encompasses two possible approaches, namely the scaffold-based and scaffold-free bioprinting. The scaffold-based approach involves the bioprinting of cells in an exogenous biomaterial, such as hydrogels or decellularized matrix components, whereas in the scaffold-free approach, cells are coaxed into forming neo-tissues and bioprinted without a support by self-assembly driving mechanisms, such as cell sorting and tissue fusion (Datta et al., 2017). Moreover, there are two directions for generating artificial blood vessels, namely the generation of interconnected vessel systems and channels, or the generation of individual vascular conducts (Maina Renee et al., 2018).

The scaffold-based bioprinting implies two main additive manufacturing concepts, namely indirect and direct bioprinting, which can be used individually or combined. Indirect bioprinting is based on printing a sacrificial material that provides the structural support for the subsequent cellularization. By contrast, in direct bioprinting, cells are loaded into the bioink containing biochemical and biophysical cues (Garreta et al., 2017) prior to the printing process. The direct method necessitates a rapid gelation or crosslinking to ensure a stable structure (Richards et al., 2017). The main techniques for blood vessel bioprinting are inkjet-based, laser-based, and extrusion-based, although other methods, such as digital stereolithography and syringe-based deposition, are available. Naturally, each technique is characterized by specific advantages and disadvantages which must be considered for the intended application (Melchiorri and Fisher, 2015). Other

categorization of the bioprinting methods include sacrificial bioprinting, embedded bioprinting, hollow tube bioprinting, and microtissue bioprinting (Hu and Zhang, 2018).

To produce cell-laden tissue constructs, the bioprinter must allow for the combination of the three main techniques, simultaneous deposition of at least two types of materials and cells and interchange of the material cartridges during the printing process, control of the temperature and pressure for the printing heads and substrate, optical monitoring of the process, accurate calibration of the needle tip position, light-crosslinking the constructs, and sterile conditions (Garreta et al., 2017). Moreover, the fabrication of cell-laden constructs through bioprinting methods require sufficient resolution in order to provide oxygen and nutrients supply by allowing for the incorporation of interstructural spaces (Richards et al., 2017).

Additionally, the direct bioprinting allows for the development of vascular networks by dispensing the bioink containing endothelial cells in the form of strands. Therefore, the cells will subsequently proliferate and differentiate to form capillary blood vessels. As the network might not be completely connected, coaxial bioprinting has been explored for the development of lumen-containing strands, termed as shell-core filaments (X. B. Chen, 2019).

The limitations associated with the synthetic vascular grafts, such as the use of materials that are not approved by the Food and Drug Administration, reduced vasoreactivity, decreased long-term patency rates (Bornstädt et al., 2018), and biocompatibility (Moldovan, 2018), has led to the intensive research work for the development of cell-only approaches for vascular tissue engineering. Therefore, tissue spheroids, cell sheets, and tissue strands without artificial stabilization have been applied for vascular graft development (Bornstädt et al., 2018, Ovsianikov et al., 2018). Furthermore, by using only patient-derived cells, fully autologous constructs can be obtained (Moldovan, 2018). Common methods for obtaining these bioconstructs include hanging drop, pellet culture or conical tube, micro-molding, microfluidics, liquid overlay, spinner flask, and rotating wall vessel techniques (Ozbolat, 2015).

The generation of vascular constructs is based on the ability of endothelial cells to self-assembly into blood vessels without tubular supports (Yee Ng et al., 2018, Ovsianikov et al., 2018). The capacity of these building blocks to fuse into cohesive constructs and further produce the extracellular matrix can be modulated by applying the magnetic or mechanical microneedles, also known as the Kenzan needles, methods (Moldovan, 2018, Ovsianikov et al., 2018).

However, the scaffold-free bioprinting method is still challenged by insufficient mechanical strength, slow cell growth, long maturation time (Hussain and Butcher, 2018), and limited control over the distribution and growth of vascular channels (Yee Ng et al., 2018).

4. CONCLUSIONS AND FUTURE PERSPECTIVES

Vascular grafting remains one of the major concerns in regard to patient compliance and survival. As the prevalence of cardiovascular diseases is continuously rising, the need for developing artificial grafts is fundamental. Although autologous grafts represent the gold standard, they are characterized by several disadvantages, such as limited availability, size mismatch, and donor site morbidity. Similarly, artificial vascular grafts present considerable limitations in terms of biocompatibility, thromboreactivity, and poor patency rate. Therefore, present research work is focused on tissue engineered vascular grafts, which might offer the solution for vascular grafting. Currently, there is no ideal solution and the vascular tissue engineering strategies must be further improved. Thus, artificial blood vessels that mimic the native tissue are still far from being developed and further work must be performed in this area.

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6. CONFLICTS OF INTEREST

The author declares no conflict of interest.