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Hemocompatible tissue-engineered vascular grafts using adult mesenchymal stem cells

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Abstract

Vascular tissue engineering can now produce compliant and durable vascular grafts to address limited supply of autologous vessel grafts for patients with coronary artery disease. Due to the demand for an anti-thrombogenic luminal surface, mesenchymal stem cells (MSCs) have been investigated for their potential to differentiate into an endothelial phenotype. This can be done through several types of chemical and biomechanical stimulation. Adipose-derived MSCs are of particular interest because they present an autologous source of sufficient MSCs to seed a monolayer onto the lumen of a typical coronary bypass graft. This review provides an overview of recent developments in endothelial differentiation methods of MSCs and main findings, as well as perspectives on future research.

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Introduction

Cardiovascular disease and standard of care treatment

Cardiovascular disease is the leading cause of death globally, claiming more than 17.3 million deaths in 2013, expected to increase to more than 23.6 million by 2030. Coronary heart disease is the most common type of cardiovascular disease [1]. Despite advances in percutaneous coronary intervention and stent technology, coronary artery bypass grafting (CABG) is still performed, especially for complex lesions (high or intermediate SYNTAX scores) [2]. There were 202,900 CAB grafts operated in the U.S. in 2012 [3].

Both arteries and veins have been used as autologous CAB grafts. The internal mammary artery (IMA) graft has been shown to have superior patency (10-year patency >90%) [4–6] with use of the left IMA yielding better survival rates [7,8]. Despite the superior patency rate of IMA, saphenous vein grafts are also commonly used for CABG patients [9] due to higher complications (e.g. mediastinitis) associated with removal of IMA [10]. About 50% of saphenous vein grafts are patent 10 years after CABG [11]. The failure of these grafts once patency is lost will require reoperation, but options may be limited by the availability of suitable autologous grafts. About ~30% of patients do not have suitable vein grafts (1979) due to vascular or harvested vein for prior vascular procedures [12].

Tissue-engineered vascular grafts

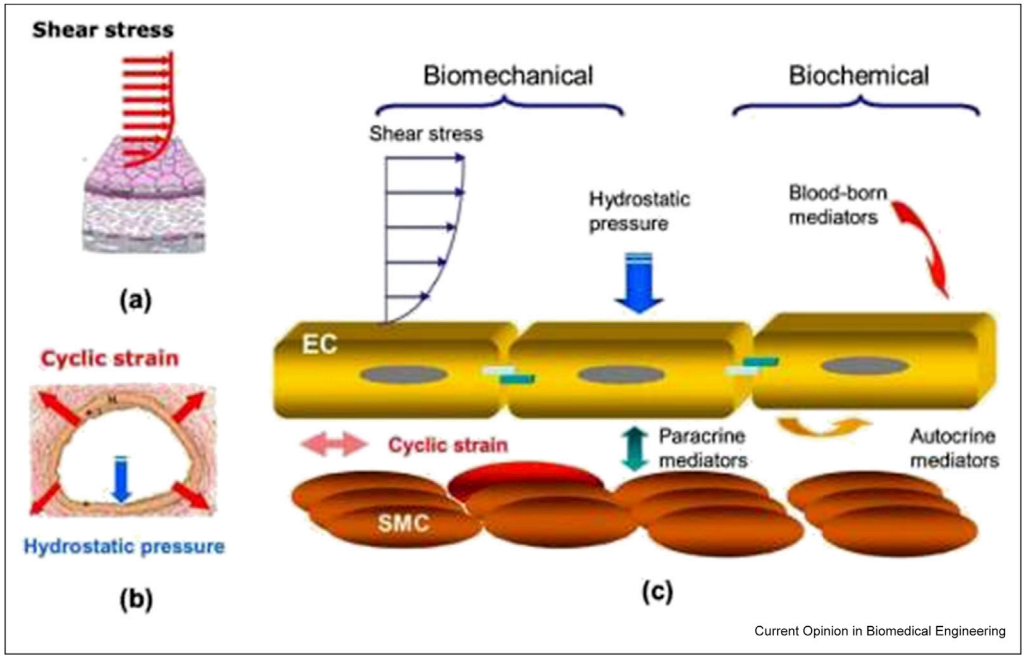
To address the problems of limited autologous vessels for use in CABG, tissue-engineering approaches for small-diameter blood vessels have been developed using some combination of cells, scaffolds, and biochemicals. Applications of TEVG are also potential solution to bypass grafts in hemodialysis and peripheral arterial disease (PAD). It is estimated that 19% of patients with end-stage renal disease use arteriovenous grafts [13] and PAD requires 45,000 bypass graft procedures yearly in the U.S [14]. The desired properties for tissue-engineered vascular grafts (TEVG) emulating those of the native artery are sufficient mechanical strength, physiological compliance, durability, infection resistance, and hemocompatibility (anti-thrombogenicity) [15]. One example is the fabrication of "tissue sheets" from smooth muscle cells (SMCs) and/or fibroblasts rolled into a fused tube that has shown high burst strength and good surgical handling [16]. Another example is production of a TEVG by entrapping dermal fibroblasts in a sacrificial fibrin gel tube, yielding tubes of cell-produced collagenous matrix with circumferential alignment as well as high burst strength [17], which have been decellularized and successfully implanted into baboons as arteriovenous grafts for up to 6 months [18]. The same success was first demonstrated with decellularized TEVG made from SMCs seeded on a

biodegradable synthetic polymer (polyglycolic acid) scaffold [19]. Although tissue engineering approach can produce the requisite mechanical properties, a strategy is needed to confer an anti-thrombogenic luminal surface to prevent thrombosis upon implantation. Strategies to confer an anti-thrombogenic luminal surface can be classified into (1) chemical treatment of the surface to mitigate thrombosis and/or induce spontaneous endothelialization, and (2) seeding of the surface with cells that are anti-thrombogenic. These two approaches can also be combined. Surface modifications of the lumen have some disadvantages, such as short half-life of anti-thrombotic moieties [20] and lack of endothelial selectivity of immobilization moieties [21]. Pre-seeding TEVG with conditioned non-thrombogenic cells holds the potential to improve hemocompatibility. This review will thus focus on the cell-based approach (2) within the last five years.

Role of endothelial cells in hemocompatibility

A thin layer (<0.2 μm) of endothelial cells (ECs) acts as a dynamic barrier on the lumen of blood vessels that is responsive to hemodynamic forces and chemical stimuli in blood (Figure 1) [22]. They are crucial in regulating hemocompatibility by preventing adhesion and aggregation of platelets leading to thrombosis. Upon vascular injury, the endothelial layer is disrupted and subendothelial matrix is exposed to blood flow. Circulating platelets adhere to the exposed matrix through specific integrins. This leads to activation of the clotting cascade through thrombin production to convert soluble protein fibrinogen to insoluble fibrin, leading to thrombus formation [23]. When the endothelium is inflamed, ECs express elevated levels of adhesion molecules such as intercellular adhesion molecule-I (ICAM-1), vascular cell adhesion molecule-I (VCAM-1), E-selectin and P-selectin that can recruit platelets and leukocytes via strong adhesion [24,25]. There are several endogenous mechanisms for ECs to prevent platelet adhesion. Glycocalyx, comprising glycoproteins and proteoglycans, is an interfacial layer between blood flow and the endothelial cell plasma membrane that regulates endothelial permeability and leukocyte interactions with ECs [26]. Studies have shown disrupting the glycocalyx layer leads to platelet adhesion to the endothelium; for example, Vink et al. damaged the glycocalyx with light-dye-induced generation of oxygen-derived free radicals and found platelets and red blood cells adhered to the vascular wall [27]. ECs of every blood vessel co-release two vasoactive hormones-nitric oxide (NO) and prostacyclin-that are inhibitors of platelet activation and vasoconstriction [28]. NO

Figure 1



Schematic diagram of hemodynamic forces acting on endothelial cells (EC) and smooth muscle cells (SMC) in the blood vessel wall. (a) Fluid shear stress, the tangential frictional force by virtue of blood viscosity, acts on ECs. (b) Cyclic strain exerts a circumferential stretch on arterial wall in response to cardiac contraction. Hydrostatic pressure acts perpendicularly on ECs. (c) ECs are constantly exposed to both biomechanical and biochemical stimuli, which modulate endothelial functional phenotype. The biochemical stimuli include hormones, growth factors, cytokines, and bacterial products that can be delivered via the blood or via autocrine or paracrine mechanisms. Reproduced without alteration from Ref. [22]. Note: Fig. 1 can be used without permission. https://openi.nlm.nih.gov/detailedresult.php?img=PMC2801858_CCR-4-269_F2&req=4.