Stem Cell Therapy for Endothelial Dysfunction in the Coronary Circulation
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Abstract

The endothelium is increasingly recognized as serving a critical role in maintaining circulatory homeostasis. Endothelial dysfunction is evidenced as an attenuation or exaggeration of the normal dynamic vasomotor range. Circulating endothelial progenitor cells (EPCs) are responsible for the endothelial replenishment. When EPC recruitment is insufficient after endothelial injury, endothelial pathophysiological ensues. Impaired endothelial function is associated with myriad cardiovascular diseases including coronary artery disease, atherosclerosis, hypertension, chronic heart failure, peripheral artery disease, diabetes, and chronic renal failure. Therefore, correction of endothelial dysfunction presents a therapeutic opportunity that, if met, could reduce adverse cardiovascular events. EPCs play an important role in maintaining endothelial function and might affect the progression of ischemic heart disease. The mechanisms underlying the salutary effect of EPCs involve EPC-mediated paracrine effects, EPC differentiation into endothelial cells, and promoting the repair of damaged endothelium. The implementation of EPCs is emerging as a new promising cell-based therapy for restoration of angiogenic activity in cardiovascular disease, which might be particularly beneficial. The goal of this article is to review and critically evaluate the relevant literature describing putative role of EPCs in the treatment of ischemic heart disease, especially that of the coronary arterial system, that is rooted in endothelial dysfunction.

Keywords: Stem cells; Progenitor cells; Angiogenesis; Endothelial cells; Ischemic Heart disease

Introduction

More than 3 decades ago, Furchgott and Zawadski first reported that the endothelium acted as not only a physical barrier between the blood and the interstitial space, but also an endocrine organ capable of releasing multiple substances [1]. Since that discovery, the importance of the endothelium in ischemic heart disease has been increasingly reported. Myriad molecules secreted by endothelial cells have been shown to participate in regulating vascular tone, platelet activity, the endogenous thrombolytic system, vascular inflammation, cell migration, and proliferation [2]. Endothelial dysfunction was first described in human hypertension in 1990 [3], where it was characterized by an altered balance in the release of relaxing and contracting factors; reduced production of endothelium-derived Nitric oxide (NO) and increased production of thromboxane A2, prostaglandin H2, and superoxide anion. This altered functional state leads to reduced endothelial-dependent vasodilatation and increased vasoconstrictor responses. When such an imbalance in endothelial function occurs, the dysfunction can become an important basis underlying the pathophysiological processes observed in numerous cardiovascular and endocrine/metabolic diseases.

Ischemic heart disease, often associated with sudden cardiac arrest, is the leading cause of mortality and morbidity worldwide [4]. In 2010, cardiovascular disease accounted for 34% of all deaths with an associated cost of $503.2 billion [5]. Currently, clinical management of ischemic heart disease relies upon restoration of blood flow through surgical interventions such as coronary artery bypass graft (CABG) and percutaneous Tran's luminal coronary angioplasty (PTCA), and on pharmacological therapeutics that, in most cases, only minimally lead to endothelial repair. Therefore, these treatments have but a modest influence on ischemic heart failure. Hence there is a need for therapeutic interventions that can accelerate the repair of dysfunctional endothelium in the ischemic myocardium, promote the formation of collateral circulation, and provide sufficient oxygen to the ischemic tissue, leading to improved heart function. A promising novel therapeutic option is the replacement of damaged endothelial cells. Endothelial dysfunction has been suggested to be an independent predictor of adverse cardiovascular event outcomes [6], emphasizing the important physiological role of this single layer of cells. In ischemic heart disease treatment, direct replacement of the damaged endothelial cells by stem/progenitor cells could allow re-endothelialization, as well as neo vascularization of ischemic tissues.

Development of the coronary circulation - origins of endothelial cells

During the heart’s development, the primordial heart assembles first as a tube that subsequently differentiates into a complex organ with four chambers each with muscular walls of varying thickness. As diffusion of respiratory gases, nutrients, and metabolites is limited to a few hundred microns, a dedicated coronary vascular system is essential if the heart tissue is to remain viable. The process of coronary vessel formation is highly regulated and can be divided into the following overlapping steps. The first, known as vasculogenesis, involves the de novo formation of vessels; this is followed by angiogenesis, the continued postnatal expansion during which extensive remodeling of primitive vascular clusters leads to the formation of the mature coronary circulation. Coronary vasculogenesis involves a mesenchymal process...
that eventually connects formed tubes in myocardium to the aortic root [7]. It is widely accepted that development of the epicardium is highly associated with the development of the coronary vascular system. Most studies in heart development have demonstrated that pro-epicardial cells undergo an epithelial-to-mesenchymal transition (EMT) to generate the migratory epicardium derived cells (EPDCs), which can give rise to coronary smooth muscle cells (SMCs), pericytes, fibroblasts and cardiomyocytes [7,8]. Although studies have demonstrated the important role of EPDCs in endothelial progenitor cell differentiation, the explicit origin of coronary endothelial cells is disputed [9-11]. Bone marrow (BM) derived cells, spleen-derived mononuclear cells, cord blood derived mononuclear cells, fat tissue derived stem cells, adventitial stem cells, and skeletal muscle progenitor cells all contribute to the pool of endothelial cell lineage [12]. Regardless of their origin, EPCs migrate over and into the developing heart where they assemble into the ECs that form primitive vascular clusters.

Endothelial function and dysfunction in coronary artery disease

Endothelial function and myocardial remodeling are tightly linked, assuring appropriate dilatation of coronary vasculature is crucial during elevated myocardial metabolic demand conditions [13]. Endothelium-derived nitric oxide (NO), a vasodilator, is recognized as important for regulation of myocardial perfusion with oxygen [13,14]. Products of myocardial metabolism, especially adenosine, serve important roles in blood supply to tissue demand matching [13]. Nor epinephrine, released from cardiac adrenergic nerves, acts on beta-2 adrenergic receptors on coronary vascular smooth muscle to coordinate coronary vascular resistance inversely to myocardial metabolic demand [14]. In addition to mediating vascular tone, molecules secreted by vascular endothelium participate in the development of atherosclerosis through regulation of platelet activity, the endogenous thrombolytic system, vascular inflammation, cell migration and proliferation [2]. Under increased stress, the myocardium responds by activating multiple integrative mechanisms to limit cellular injury and to repair the damaged tissues. In response to ischemia, hypoxia inducible factor-1 (HIF-1) promotes secretion of multiple pro-angiogenic growth factors, including VEGF, FLK-1, FGF-1, FGF-2 and TGF-β [15,16]. These molecules are implicated in coronary vasculogenesis. However, this adaptive mechanism is insufficient to limit myocardial injury and typically does not provide sufficiently coordinated vasculogenesis to reduce the eventual infarct size [17]. Impaired endothelium-dependent coronary flow reserve (CFR), accompanied by insufficient myocardial perfusion, contributes to ischemic heart disease [18,19] and is suggested as an independent predictor of adverse cardiovascular events [6].

Assessment of coronary endothelial dysfunction

Better characterization of the condition known as endothelial dysfunction should provide more rational diagnostic and therapeutic interventions for patients with coronary artery disease. Usually, coronary flow reserve (CFR) and so-called fractional flow reserve (FFR) following brief coronary artery occlusion are used to assess endothelial function. The gold standard for the diagnosis of coronary endothelial dysfunction is coronary angiography, followed by pressure/flow assessment with a Doppler catheter in response to intracoronary acetylcholine [vasodilatation (viable endothelium)/vasoconstrictor (endothelial dysfunction) challenge test], and CFR or FFR testing in response to intracoronary adenosine of following brief coronary artery occlusion (smooth muscle vasodilatation evaluation) [20]. Additionally, biomarkers of endothelial dysfunction expressed in plasma, such as ICAM-1, VCAM-1, and E-selectin, LOX-1, CD-40 ligand, CRP and ADMA, have been proposed [21].

During the past several decades, in vivo noninvasive diagnostic techniques have become increasingly popular, as discoveries of mechanisms underlying endothelial dysfunction in the laboratory have been translated to studies in patients. Cardiac magnetic resonance imaging (CMRI), a promising new technology without use of radiation, can be used to measure global and regional myocardial function, the ischemic region size, and scar tissue. Myriad parameters can be acquired in one imaging session [22]. Several other noninvasive techniques like positron emission tomography (PET) [23], myocardial perfusion scintigraphy—single photon emission computed tomography (SPECT) [24] and 2D Doppler echocardiography [25] using echo-contrast agents also can be used to assess coronary endothelial dysfunction.

Established drug therapy to mitigate endothelial dysfunction

Although the mechanisms underlying coronary endothelial dysfunction are often multi-faceted, treatment strategies are principally targeted at ameliorating an underlying pathology such as atherosclerosis or ischemia [26]. All pharmacological therapies are intended to restore or replace endothelial functions, reduce mortality and morbidity, and improve quality of life. As noted above, NO, released by endothelial cells, plays a crucial role in modulating myocardial perfusion by regulating the appropriate dilatation of proximal coronary vasculature in response to increases endothelial shear stress consequent to adenine-mediated distal vasodilatation. Members of the "statin" drug class (HMG co-reductase inhibitors) have been shown to improve endothelial function by lipid-independent mechanisms, involving anti-inflammatory, antioxidant properties, and to independently restore vascular NO availability [27]. Through a different mechanism, aspirin, a non-selective cyclooxygenase inhibitor, can prevent platelet aggregation at dysfunctional endothelial loci. The therapeutic effects of other drugs like beta-blockers, or calcium channel blockers (CCBs) related to mitigating endothelial dysfunction is controversial. However, carvedilol, a newer generation of beta-blocker (an alpha-1 + beta-1 + beta-2 adrenergic receptor antagonist) can mitigate the adverse side effects, such as worsening of coronary spasm derived from beta-blockers alone [28].

Putative angiogenic growth factor therapy for ischemic heart disease

The hypoxic myocardial environments consequent to progressive coronary artery disease are the loci wherein angiogenesis can be expected to occur through the expression balance of pro-angiogenic and anti-angiogenic molecules. Therefore, to improve myocardial perfusion in coronary artery disease, pro-angiogenic growth factors as either delivered as purified protein or expressed through gene therapy have been tested [29,30]. The pro-angiogenic growth factors most commonly employed have been VEGF and FGF-2, heparin-binding endothelial cell mitogens. To date, the therapeutic value of FGF-2 and VEGF-2 remains controversial, despite a substantial number of clinical trials [31,32]. One of the major limitations of this pro-angiogenic therapy may be the lack of accompanying smooth muscle myogenesis. In addition to intrinsic hypoxia, shear stress, a more important extrinsic mediator is required for endothelium-mediated arteriogenesis. Without concomitant smooth muscle development, capillaries formed during vasculogenesis remain as endothelial tubes and decline with time even under shear stress conditions [8]. Other putative mediators or angiogenesis continue to be proposed. For example, caveolin-1, a contributor to eNOS mediated NO release during shear stress has
been suggested as a putative therapeutic agent [33]. Additionally, the potential of thymosin β4 (Tβ4) to restore heart function after ischemia was first reported in 2004 [34]. Tβ4 demonstrated to participate in coronary vasculogenesis, angiogenesis and arteriogenesis [35].

**Endothelial progenitor cell-based therapy for endothelial dysfunction**

Limited endothelial regeneration and impaired angiogenesis are involved in the progression of coronary artery disease and complications. Currently, the beneficial effects of pharmacological agents and growth factors on the pathogenesis of endothelial dysfunction are limited. However, a growing body of preclinical data suggests that a stem/progenitor cell-based approach may hold promise, as a treatment that can directly restore function to the endothelium and damaged tissue. Currently, there are seen to be two distinct categories of stem cells in animal models and humans: (1) embryonic stem cells; and (2) non-embryonic, “adult” or “somatic” stem/progenitor cells, which derive from any body tissue except for gametes. Several of these cell types have been shown to increase the functional recovery of the heart after ischemia by physically forming new blood vessels, or alternatively by providing pro-angiogenic and anti-angiogenic factors promoting tissue repair in a paracrine manner.

A promising new therapy for endothelial function is emerging from the discovery of EPCs. In the 1990’s, the discovery of circulating EPCs led to our current understanding of how bone marrow-derived cells contribute to physiological or pathological neovascularization [36,37]. A study performed by Fujiyama et al. [38] revealed that functional restoration of endothelium resulted from transplanted EPCs, which was confirmed by the release of NO, along with inhibited functional restoration of endothelium resulted from transplanted [36,37]. A study performed by Fujiyama et al. [38] revealed that cells contribute to physiological or pathological neovascularization EPCs led to our current understanding of how bone marrow-derived repair in a paracrine manner.

Approaches to enhance EPCs migration and homing by selective growth factor expression

Although EPC number and function are known to be highly linked with cardiovascular risk factors, mechanisms underlying the decreased circulating EPCs in coronary artery disease remain unclear. Several reports have indicated that stoma-derived factor-1α (SDF-1α) and its G protein–coupled receptor CXCR4 are essential for promoting hematopoietic progenitor cell recruitment and angiogenesis [57,58]. Carr et al. [59] demonstrated that administration of SDF-1α could stimulate CXCR4 receptors expressed on EPCs and bone marrow stem cells (BMCs), and thereby act as a chemo tactic and pro-migratory factor. Our recent study reported that over expression of CXCR4 facilitated mobilization and engraftment of MSCs, leading to enhanced angiogenesis [60]. Other mobilizing factors, such as G-colony stimulating factor (GCSF), VEGF and erythropoietin (Epo) were reported to enhance EPCs mobilization, proliferation and homing, which can activate the Akt protein signaling pathway and endothelial nitric oxide (eNOS) secretion [61]. In a phase I/II clinical trial, the salutary therapeutic angiogenic effects of GCSF-mobilized CD34+ MSCs has been demonstrated in patients with intractable critical limb ischemia [61]. Moreover, the CXCR4 inhibitor AMD3100 is now FDA-approved to mobilize EPCs; an efficient therapeutic effect in human coronary artery disease (MI) has been proven [62].
Differentiated ECs from stem/progenitor cells and their surface markers

One of the challenges to stem cell therapy is the limited supply of postnatal stem cell sources. Both ESCs and iPSCs have been used to generate unlimited numbers of genetically identical functional cells for therapy for ischemic disease, but using iPSCs for cell-based therapies and transplantation can obviate the ethical issues and potential for allogeneic immune responses to ESCs. Importantly, Yamanaka et al. have recently generated iPSCs derived from individual human Japanese subjects bearing 50 different haplo types, which are compatible with the immune system in 90% of the Japanese population [63], in a novel cell-based approach to the emerging field of personalized medicine. However, due to the high differentiation potential of ESCs and iPSCs, protocols must be developed so as to guide and refine the isolation and differentiation of ESCs or iPSCs before human transplantation of these cells.

Endothelial cell (EC) differentiation from stem/progenitor cells is a complicated process, governed by various molecular signaling pathways. In vitro, derivation of vascular cells can be triggered by a variety of conditions, including co-culturing with other cells lines as described below, or culturing in other defined conditions including specific mixtures of cytokines, genetic engineering, and manipulation of micro environmental conditions including the extracellular matrix (ECM) and the use of shear stress.

Currently, no standardized protocol exists for differentiating stem/progenitor cell derived endothelial cells. To increase the differentiation efficiency of spontaneous EB-differentiation from ESCs/iPSCs, techniques such as co-culture with mouse embryo fibroblasts [64], OP9 [65], S17 [65,66], MS-5 [65], and mouse ECs [66] prior to sub-culture have been performed. However, in such experiments, the positive ECs only accounted for 10% of the total cell population. Recently, other improvements on EB-based protocols have been reported including addition of VEGF-A [67], hypoxia induction [68] and TGF-β [69] signaling pathway suppression. Kane et al. [70] have successfully developed a direct EC differentiation method, which can generate functional ECs from human ESCs in a serum-free and feeder free manner. Animal models have demonstrated the therapeutic effect of these cells in vivo. Thus, this differentiation protocol can be potentially used for ischemic disease treatment in clinic.

The combination of multiple EC-specific markers and functional analysis selective for ECs is necessary for derivation and identification of stem/progenitor cell-derived ECs. Many bio-markers, such as Dil-labeled acetylated low density lipoprotein (Dil-Ac-LDL) uptake, CD31, VEGF-R1 or Flt-1, VEGF-R2 or Flk-1/ KDR, VCAM-1/CD106, VE-cadherin/CD144, endothelial nitric oxide synthase (eNOS), vWF, Tie1, and Tie2, are functionally important for endothelial formation, maintenance and remodeling [63]. However, since VEGF-R2 is expressed in both iPSCs [66-71] and in ECs [72], it cannot be used to specifically identify ECs differentiation. We recently demonstrated that over expression CXCR4 [60] or NPY stimulation can increase differentiation of stem/progenitor cells into ECs [73].

Importantly, it has been demonstrated that EPCs can differentiate into VSMCs [74]. Vascular smooth muscle cells (VSMCs) are important for the maturation of vasculature; they cover the outside of the endothelium of the blood vessels, and maintain appropriate blood pressure and control blood flow. The genes/markers employed for functional VSMC differentiation like alpha-smooth muscle actin (α-SMA), smooth muscle-myosin heavy chain (SM-MHC), smoothellia 22 have been recognized recently [63].

Mesenchymal stem cells (MSCs), which can be isolated from both adult and fetal tissues, are perhaps the most promising sources for therapy. These cells raise fewer ethical concerns than ESC, and are both relatively abundant and easy to prepare and expand for transplantation. MSCs, including heterogeneous cell subsets, exhibit multi-lineage differentiation potential [75-77], yet, controversy exists regarding their efficacy as a cell-based therapeutic platform. The clinical application of MSCs has raised concerns regarding their safety with respect to tumor formation and immune rejection. Nevertheless, preliminary results from the use of MSCs in clinical trials showed improved left ventricular function [78,79].

Cell delivery

The number and migration of circulating EPCs have been shown to be bio-reporters for endothelial dysfunction in cardiovascular disease [80]. It has been demonstrated that endothelial injury accompanied with insufficient circulating EPCs is associated with progression of cardiovascular sequelae. Several methods, including intravascular injection and direct tissue injection into the infarcted myocardial region, are used currently to deliver cell-based therapies. Stem/progenitor cell homing to infarcted region is limited by multiple factors, including long circulation time, coronary blood flow, intra venous and left ventricular blood flow. Therefore, determining the optimal, most efficient cell delivery method to injured coronary vasculature and myocardium is vital for the potential of regenerative medicine to be realized.

Intracoronary Application of Stem/Progenitor Cells

Non-invasive intravenous delivery of stem/progenitor cells is an attractive technology easily achieved in the clinic, where repeated administration of cell-based therapy can occur [81]. Intracoronary delivery of stem/progenitor cells has revealed a cardiac retention of a relatively small fraction (1.3% to 2.6%) of cells after administration of bone marrow cells (BMCs) [82]. BMCs contain several cell sub-populations including hematopoietic stem cells, mesenchymal stem cells, endothelial progenitor cells and other cell populations. Meta-analyses of several clinical trials has concluded that there is an absolute increase of 3% to 4% in the ejection fraction of the left ventricle after intracoronary infusion of autologous BMCs [83] however, this salutary effect is reduced when patients were re-evaluated at 12 months after cell administration [84].

Intra myocardial application of stem/progenitor cells

End-cordial injection of stem/progenitor cells is used to deliver stem/progenitor cells to the myocardium [85]. Although this retrograde intra-arterial catheter technique is considered a safe and minimally invasive method for possible cell-based therapy of chronic ischemic heart disease [86], injections in unintended locations, unintended cell loss into the ventricular chamber and undesired ventricular arrhythmias of ventricular origin can occur during and after cell transplantation [87]. Intra myocardial stem/progenitor cell injection in combination with coronary artery bypass graft (CABG) surgery has been performed in a well-exposed ischemic area, which allowed for repeated injection within different sites in the peri-infarction border zone of the regionally infarcted left ventricle with a small gauge needle [88-90]. Recent reports reveal that this method appears to overcome some limitations of endo-cordial intra myocardial injection and results in a high stem cell persistence, engraftment and re-vascularization [88-91].
Tissue engineering for cardiovascular disease

A recent development in cell-based therapy is the incorporation of established principles and techniques used in diverse applications of tissue engineering. This merger offers the promise of functional tissue creation for therapeutic application in cardiovascular disease, offering approaches to increased stem/progenitor cell delivery efficiency through both increased numbers and survival of transplanted cells [92].

New vessel formation has been reported in Matrigel cell sheets seeded with a combination of human endothelial and umbilical cord blood-derived mesenchymal progenitor cells [93]. The addition of fibroblasts can effectively promote angiogenesis, improve survival of seeded cells, and subsequently result in heart functional restoration [94,95].

For coronary artery syndromes and disease, assuring that transplanted stem/progenitor cells survive in the ischemic microenvironment is challenging because of the severely compromised oxygen and nutrient supply. Porous collagen matrix seeded with EPCs and MSCs applied onto the epicardium after MI, has been reported to promote angiogenesis and increase cell survival [96]. In heart development, angiogenesis is intimately linked with myocardial growth and remodeling. Impaired angiogenesis, known to contribute to impaired coronary collateral vessel formation [97], is correlated with reduced left ventricular ejection fraction [17,98]. We recently have reported the development of strategies to engineer a vascularized cell sheet comparable to native myocardium [99] using a tri-cell culture, with growth factors, selective gene expression manipulations and novel pro-angiogenic scaffolds. Engineered 3-D neonatal cardiomyocyte sheets containing pre-formed EC networks promoting capillary formation were associated with attenuated left ventricular remodeling [54]. In addition, the application of pre-vascularized cardiac tissue patches with modified iPSCs showed more myocardial-like passive mechanical properties and higher cell survival, and led to improvements in left ventricular mechanical performance [100]. To support the integration of transplanted cells into injured myocardium so that contractile performance of the heat would be improved, some new materials like PEG hydro gels [101], polymer nanofibers [102] or combinations of ECM and polydimethylsiloxane (PDMS) films [103] have also been used.

Another reported method for engineering functional replacement tissue is achieved by seeding stem/progenitor cells on temperature sensitive dishes, which can release cell monolayers by alteration the hydrophobic/hydrophilic switch of the surface. Effective revascularization in the ischemic tissues has been confirmed using human smooth muscle cell (SMC) seeded temperature sensitive sheets [104].

Both peritoneum and omentum have been reported clinically to promote wound healing and to stimulate revascularization of ischemic tissues [105,106]. Six decades ago, O’Shaughnessy was first to report cardio-omentalpexy procedures in which pedicled omental grafts were used to provide a vascular supply for the epicardial surface of ischemic human hearts. Recently, we have successfully developed a tri-cell seeded peritoneal patch, which resulted in the functional development of collateral circulation from the cell patch to the native coronary arteries in association with enhancement in left ventricular function after MI [99]. Native biomaterials used as substrates are an attractive option when used in combination with stem/progenitor cells and have demonstrated such favorable and desired outcomes as improved cardiac contractility (via direct myogenesis or due to paracrine effects from stem cells), enhanced tissue nutrition (via angiogenesis), and enhanced cell survival (via anti-apoptosis), which combine to reduce or reverse myocardial remodeling, limit infarct size and improve the heart’s mechanical performance. Furthermore, by combining genetic engineering with cell therapy, it may be possible to enhance the regenerative capacity of these stem/progenitor cells, which is particularly relevant in the context of adult autologous cell therapy, and to therefore provide additional benefits that may overcome many of the limitations of cell or gene therapy alone.

Conclusions

The endothelium plays an essential role in maintaining circulatory homeostasis by the release of factors that relax and contract vascular smooth muscle and assure appropriate blood flow to tissues, including the myocardium. Any change in the vasomotor regulatory balance may be characterized, at least in part, as endothelial dysfunction that leads to impaired control of vascular tone and may seminally participate in the pathogenesis of myriad cardiovascular diseases. This review summarizes evidence for endothelial dysfunction in cardiovascular diseases and overview relevant to the important role of EPCs in treatment of cardiovascular diseases especially in coronary artery disease. A better understanding of the mechanism(s) of endothelial dysfunction may expose new preventive strategies to reduce cardiovascular morbidity and mortality.

Despite the promise of such therapies, much work remains to be done before alternative treatments for endothelial dysfunction-related cardiovascular disorders will be widely available to patients. The challenge ahead lies in identifying specific unique mechanisms or more likely networks of articulated mechanisms that are responsible for tissue responses to various drugs and cell-based therapy. Although novel approaches directed at neovascularization and focused on ameliorating aspects of endothelial dysfunction are rapidly advancing, many challenging questions remain regarding the precise mechanisms involved in vascularization of the heart, including coronary vasculature origin, vascular cell fate, vessel growth, and maintenance. Future studies aimed at optimal technology for specific stem/progenitor cell applications, the best cell types, and improvements in cell delivery techniques are needed in order to develop clinically relevant approaches.

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