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Review Article

Tissue-engineered amniotic membrane in the treatment of myocardial infarction: a systematic review of experimental studies

Gustavo Gavazzoni Blume, Paulo André Bispo Machado-Júnior, Giovana Paludo Bertinato, Rossana Baggio Simeoni, Julio César Francisco, Luiz César Guarita-Souza

Division of Cardiovascular Diseases, School of Medicine, Catholic University, Curitiba, Paraná, Brazil

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Abstract: Objective: myocardial infarction (MI) remains the leading cause of death worldwide. Cell-based therapies have become potential therapeutic approaches, attempting to recover the contractility of necrotic cardiomyocytes. In the present study, we aimed to systematically evaluate experimental studies on the use of tissue-engineered amniotic membrane (hAMC) in MI treatment. Methods: a systematic review of literature published in PubMed, Embase and CENTRAL databases was conducted, until March 31, 2020, for experimental studies reporting on hAMC cell-therapy performed on LV function, MI size, paracrine effects, angiogenesis, and cell differentiation. Two reviewers selected the articles that met the inclusion criteria and disagreements were solved through a consensus. Results: a total of 11 studies were included for data extraction. For the acute scenario, therapeutic use of hAMC after MI was capable of improving LV function in rats, mainly due to its paracrine effects (anti-apoptotic and anti-inflammatory) and associated with cardiomyocyte differentiation, MI size reduction and neo-angiogenesis. Conclusion: tissue engineered hAMC following MI provided clinically relevant benefits on cardiac function and ventricular remodeling.

Keywords: Myocardial infarction, tissue regeneration, human amniotic membrane, stem cells, heart function

Introduction

Myocardial infarction (MI) and heart failure (HF) are the leading cause of death worldwide [1-3]. Current therapeutic strategies are aimed at preventing progression of left ventricular (LV) pathological remodeling after MI, with little evidence of improvement in cardiac regeneration and ventricular function [4, 5].

As an alternative, tissue engineering using human amniotic membrane (hAMC) started to be extensively used in regenerative medicine, with the aim of regenerating the injured tissue. The main hypothesis for its use is that it could serve as a possible scaffold for stem cells proliferation and differentiation, with an added potential of anti-inflammatory, antifibrotic and pro-angiogenic effects [6-13].

Previous studies have investigated the potential use of hAMC after myocardial ischemia, evaluating its consequences in global cardiac function. Despite this, the exact mechanisms underlying this association and its capacity to improve cardiac function and reduce LV remodeling are still controversial. This study set out to systematically review experimental studies appraising the impact of hAMC in the post-infarcted heart.

Materials and methods

Information sources

We searched for experimental studies that aimed to evaluate the use of hAMC in the treatment of MI. Electronic searches were conducted, without language restrictions, through PubMed, Embase, and The Cochrane Central Register of Controlled Trials (CENTRAL), from September 1, 2019 until March 31, 2020. Combinations of words related to “human amniotic membrane” and “amniotic fluid” were included as search terms in all databases with each of the following words: “myocardial infarc-

tion", "myocardial ischemia", "acute myocardial infarction", "experimental studies" and "animal model". Citations were initially selected at the title/abstract level and compliance with inclusion criteria was assessed in the complete manuscript.

Risk of bias

For quality assessment of the studies, we used the SYRCLE's risk of bias tool (**Table 1**). Internal validity was appraised by separately addressing the risk of selection, performance, adjudication, and attrition bias. Study search, selection, and appraisal were performed by two independent investigators (Blume GG and Machado-Junior PAB) with disagreements solved by a third reviewer (Guarita-Souza LC).

Eligibility criteria

Experimental randomized and non-randomized studies assessing the tissue-engineered use of amniotic membrane (injectable or as a patch) for the treatment of myocardial infarction were included. Main outcomes assessed were improvements in cardiac function, ventricular remodeling, tissue fibrosis, angiogenesis, and inflammatory proprieties. Exclusion criteria comprised irretrievable or unclear data, duplicate reports, ongoing or unpublished data, and studies comprising other scenarios than myocardial ischemia. Letters, editorials, and studies using other cell-types than hAMC were also excluded.

Results

Literature review

Twenty-eight citations were retrieved from the database searches. Ten articles were excluded for being duplicates. The remaining 18 articles were assessed according to the aforementioned criteria. Seven articles were excluded because the topics did not fully match the eligibility criteria, resulting in a total of 11 studies included in the review (**Figure 1**). The 11 articles and their main findings are described in **Table 2** and **Figure 2**. A comprehensive analysis of the papers is shown in **Table 3**.

Intervention methods

In vivo and in vitro analyses were used to access the effectiveness of hAMC on infarcted hearts. Two main techniques were chosen for in vivo analyses: injection of hAMC hydrogels in the infarcted area or transplantation of a hAMC patch into the MI area. The choice over either of the techniques was mainly due to the experience of the authors. The possible benefits of hydrogels or a patch were not assessed in the studies [14-22]. The theorical benefit for using patch implants over hydrogels, hypothetically mentioned by Khorramirouz et al., is based on the fact that patches could serve as a three-dimensional structure capable of carrying stem cells with better delivery and retention properties, adding biocompatibility, structure resemblance, mechanical strength, large surface area-to-volume ratio, and high porosity in the absence of immunological reactions [22, 23].

LV function

Assessment of LV function was usually performed with echocardiography by measuring ejection fraction (EF) and fractional shortening. Although results from Gorjipour et al. did not show improvement in cardiac function as assessed by echocardiographic parameters in a chronic MI model [24], Henry et al., using a similar delivery approach, demonstrated an almost 10% improvement in ejection fraction when compared to the acute phase of infarction [16]. Roy et al., using a catheter-based pressure-volume curve to assess LV function, suggested that the use of a hAMC patch in the ischemic area might prevent pathological ventricular remodeling, thereby improving global cardiac function [18]. In another comprehensive article from Roy et al., LV function was assessed through MRI and Specke Tracking echocardiography, showing a significant improvement in ejection fraction and strain rate when compared to controls, 4 weeks after the MI [19]. In 2009, Fujimoto et al. analyzed fractional area change as a measure of LV function and evidenced an improvement 6 weeks after coronary ligation when compared to controls [25].

MI size

Four of the 11 studies analyzed infarct size and its relationship to the therapeutic use of hAMC. Fang et al., using Masson's trichrome staining and a digital image analyzer, described a reduction of the infarcted area four weeks after hAMC injection. Three rats in each group were used for the analyses and the infarcted area was measured as a percentage of the injured area divided by the whole ventricular area and

Table 1. SYRCLE's risk assessment bias tool

AUTHOR	SEQUENCE ALLOCATION	GROUPS SIMILAR AT BASELINE	ALLOCATION CONCEALMENT	ANIMALS RANDOMLY HOUSED	INVESTIGATORS BLINDED FOR INTERVENTION	RANDOM OUTCOME ASSESSMENT	OUTCOME ASSESSOR BLINDED	INCOMPLETE OUTCOME DATA	FREE OF SELECTIVE OUTCOME REPORTING	FREE OF OTHER SOURCES OF BIAS
Henry et al. [16]	Yes	Yes	Un	Un	Un	Un	Un	Un	Yes	Yes
Gorjipour et al. [24]	Yes	Yes	Un	Un	Un	Un	Yes	Un	Yes	Yes
Khorramirouz et al. [22]	Yes	Yes	Un	Un	Un	Un	Yes	Yes	Yes	Yes
Roy et al. [18]	Yes	Yes	Un	Un	Un	Un	Yes	Yes	Yes	Yes
Danieli et al. [14]	Yes	Yes	Un	Un	Yes	Un	Yes	Yes	Yes	Yes
Song et al. [20]	Yes	Yes	Un	Un	Un	Un	Un	Un	Yes	Yes
Roy et al. [19]	Yes	Yes	Un	No	Un	Un	Yes	Yes	Yes	No
Kim et al. [17]	Yes	Yes	Un	Un	Un	Un	Yes	Un	Yes	Yes
Fang et al. [15]	Yes	Yes	Un	Un	Un	Un	Yes	Un	Yes	Yes
Tsuji et al. [21]	Yes	Yes	Un	Un	Un	Un	Yes	Yes	Yes	Yes
Fujimoto et al. [25]	Yes	Yes	Un	Un	Un	Un	Un	Yes	Yes	Yes

Un = Unknown, due to lack of data.

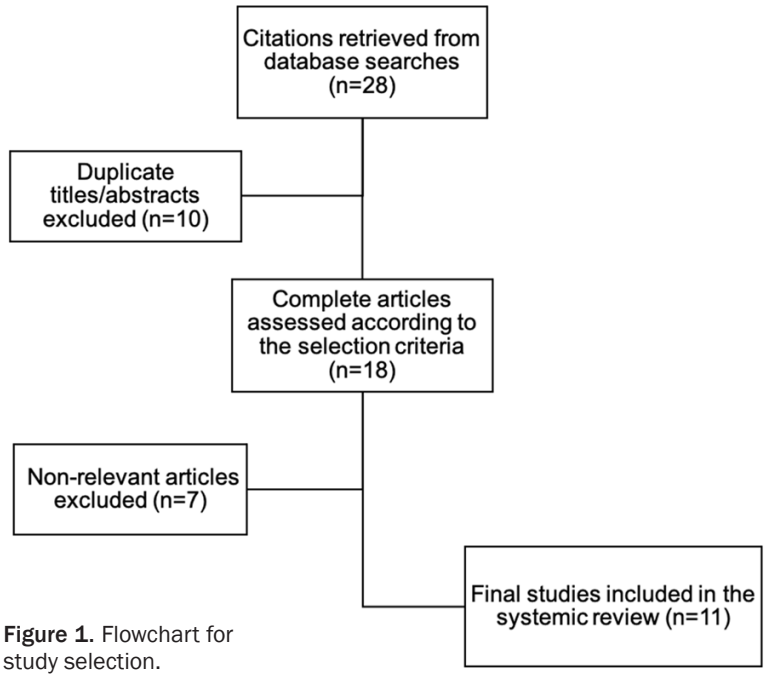

Figure 1. Flowchart for study selection.

averaged by sections. The infarcted area was significantly reduced in the amniotic membrane group when compared to controls (32% vs. 39.6%, P<0.05) [15]. Likewise, Henry et al. observed that the MI area was significantly reduced by the therapeutic use of hAMC five weeks after myocardial infarction [16]. On the other hand, using a similar methodology, Roy et al. did not find a statistically significant difference in the MI area when compared to controls after four weeks [19]. In 2015, Danieli et al., using immunohistochemistry methods, observed that intramyocardial injection of concentrated hAMC-CM was capable of limiting the MI area by 28.5% (P = 0.01), when compared to controls, after 48 hours in an ischemia-reperfusion model [14].

Paracrine effects

Higher levels of angiogenin, epidermal growth factors, interleukin 6, interleukin 8, and monocyte chemoattraction proteins were found in hypoxic mice and rats treated with hAMC, which may explain the functional improvements related to the paracrine effects behind hAMC use [19, 20]. Prevention of cell death, increased cell viability, upregulation of anti-apoptotic genes, downregulation of pro-apoptotic factors, and reduced inflammation have also been associated with the use of hAMC after myocardial infarction. Danielli et al., in an ischemia-reperfusion model study, suggested that hAMC might reduce nuclear fragmentation and caspase activation hence protecting cardiac-like cell injury [14, 22].

Angiogenesis

In vitro and in vivo analyses have shown an increase in the pro-angiogenic effect of hAMC as a result of the following proteins: vascular endothelial growth factor, granulocyte chemotactic protein, neutrophil activating protein, interleukin 8, thrombopoietin, platelet-derived growth factor, basic fibroblast, and insulin-like growth factors [14, 17, 19, 20]. An analysis conducted with Masson's trichrome staining and immunohistochemistry have also demonstrated an increase in number and diameter of the vessels in the infarcted area of animals treated with hAMC [19]. Khorramirouz et al., using a patch-based intervention model, confirmed the angiogenesis capacity through an increased number of $CD34^+$ cells in the patch-implanted group when compared to the control group [22]. Controversial results were found by Tsuji et al., suggesting that neovascularization may not play a role in the improvement of cardiac function, mainly due to the fact that, in their study, hAMC did not affect capillary density [21].

Cardiac differentiation

The cardiomyocyte differentiation potential of hAMC was analyzed in six of the 11 studies. Tsuji et al. suggested that hAMC differentiates into cardiomyocytes in vitro and in vivo, without any epigenetic agent or gene transfer, and with a higher efficiency when compared to stem cells [21]. Immunohistochemistry analyses used by Fang et al. demonstrated cardiomyocyte differentiation of hAMC [15]. Despite a positive differentiation, the authors stated that the small number of cardiomyocytes present in the sample was insufficient to explain the process of recovery from MI [15]. Desmin-positive cells, abundantly present in the patch-implanted

Table 2. Main points

Study	Year	Design	hAMC Intervention Method	Primary End Point	End Point Analysis
Henry et al.	2019	Experimental	Injection of hAMC into MI area	LV Function and MI Size/Fibrosis	Echo and Histological analyses
Gorjipour et al.	2019	Experimental	Injection of hAMC around the ischemic area	LV Function, Fibrosis, and Differentiation	Echo, histological analyses, and immunohistochemistry
Khorramirouz et al.	2019	Experimental	hAMC patch into MI area	LV Function, Fibrosis, and Differentiation	Echo, histological analyses, and immunohistochemistry
Roy et al.	2016	Experimental	hAMC patch into MI area	LV Function	LV Pressure-Volume curves
Danieli et al.	2015	Experimental	Injection of hAMC around the ischemic area	MI size and Paracrine effects	In vivo and in vitro analyses of angiogenesis, cardioprotection, and MI area
Song et al.	2015	Experimental	In vitro hypoxic condition and in vivo injection of hAMC into MI area	Paracrine effects	In vivo and in vitro analyses of angiogenesis, cardioprotection (Cytokines-ANG, EGF, IL-6, MCP-1)
Roy et al.	2015	Experimental	Injection of hAMC in the peri-infarct area	LV Function, Paracrine effects, and MI Size	MRI, Speckle tracking Echo, histological analyses, and immunohistochemistry
Kim et al.	2013	Experimental	In vitro hypoxic condition and in vivo injection of hAMC into the border zone of infarct area	LV function and angiogenesis	Echo, histological analyses, polymerase chain reactions, chemotaxis, and adhesions assays
Fang et al.	2012	Experimental	Injection of hAMC and stem cells into MI area	LV Function and MI Size	CT, histological analyses, immunohistochemistry, myocardial protein and gene expression
Tsuji et al.	2010	Experimental	In vitro hypoxic condition and in vivo injection of hAMC into border zone of MI	LV Function, Fibrosis, and differentiation	Echo, histological analyses, immunohistochemistry, and polymerase chain reactions
Fujimoto et al.	2009	Experimental	In vitro hypoxic condition and in vivo injection of naïve-rat amniotic membrane in the border of MI area	LV Function and paracrine effects	Echo, histological analyses, immunohistochemistry, and polymerase chain reactions

ANG-angiogenin, CT-computed tomography, EGF-epidermal growth factor, hAMC-decellularized human amniotic membrane, IL-6-Interleukin, LV-left ventricle, MCP-1-monocyte chemoattractant protein, MI-myocardial infarction, MRI-magnetic resonance imaging.

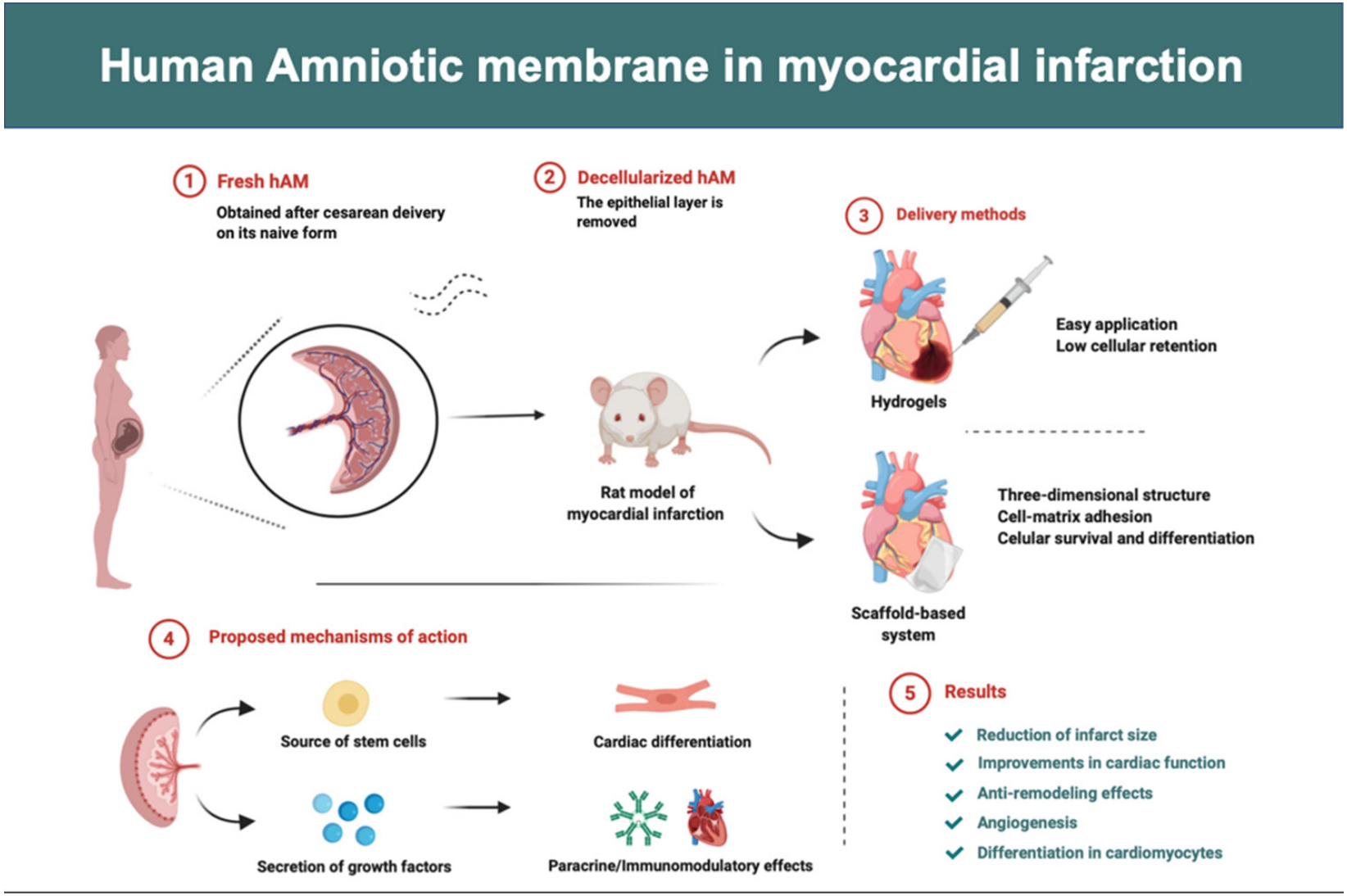

Figure 2. Main findings of the studies. The hAM is obtained from patients undergoing cesarean delivery, and it can be used on its (1) naïve or (2) decellularized form. In rat models of myocardial infarction, hAMC can be delivered through cardiac injection as a hydrogel or as a patch in the infarcted area (3), and it may act through cardiac differentiation and immunomodulatory and paracrine effects (4). The most commonly observed results so far are reduction of infarct size, improvements in global cardiac function, angiogenesis, and differentiation into cardiomyocytes.

Table 3. Comprehensive analyses

Title	Author	Journal	Year	Study Design	Country	Hypothesis	Primary Outcome	Animal	Intervention	Results
Development of Injectable Amniotic Membrane Matrix for Postmyocardial Infarction Tissue Repair.	Henry et al.	Adv.Health Mater.	2019	Experimental	EUA	Demonstrate the feasibility of injectable hAMC matrix and its efficacy in attenuating degenerative changes in cardiac function after MI	Cardiac function by echocardiography and MI Size	Rat	Injection of hAMC	Reduction in MI size and significant improvement in LV ejection fraction
Mesenchymal stem cells from human amniotic membrane differentiate into cardiomyocytes and endothelial-like cells without improving cardiac function after surgical administration in rat model of chronic heart failure.	Gorjipour et al.	J Cardiovasc Thorac Res.	2019	Experimental	Iran	Efficacy of hAMC for the treatment of heart failure related to chronic ischemia	Cardiac function by echocardiography, tissue fibrosis by Masson's trichrome, immunohistochemistry for angiogenesis and troponin T markers for differentiation	Rat	Injection of hAMC	No improvements in cardiac function and cardiac fibrosis; positive markers of differentiation into vascular endothelial cells and cardiomyocytes
Evaluating the efficacy of tissue-engineered human amniotic membrane in the treatment of myocardial infarction.	Khorramirouz et al.	Regen Med.	2019	Experimental	Iran	Efficacy of hAMC in the treatment of myocardial infarction lesions	Histology and immunohistochemistry for cell regeneration, angiogenesis and reduction of fibrosis and inflammation after 14 days	Rat	Patch of hAMC	Positive markers for cardiac differentiation into cardiomyocytes and neovascularization, reduced inflammation, apoptosis and fibrosis
Decellularized amniotic membrane attenuates postinfarct left ventricular remodeling.	Roy et al.	J Surg Res.	2016	Experimental	Germany	Evaluate the effects of naïve and decellularized hAMC on post-ischemic LV geometry and function.	Cardiac function by LV pressure-volume curves using a conductance catheter and MI size	Rat	Patch of hAMC	Decellularized hAMC supports postinfarct ventricular dynamics independent from the actual regeneration processes
Conditioned medium from human amniotic mesenchymal stromal cells limits infarct size and enhances angiogenesis.	Danieli et al.	Stem Cells Transl Med.	2015	Experimental	Italy	Evaluate the putative paracrine mediators of hAMC on infarcted rat hearts	In vivo and In vitro paracrine effects of AM on cardioprotection and angiogenesis and infarct size	Rat	Injection of hAMC	Administration of hAMC favors the repair process after acute myocardial infarction with cytoprotective and proangiogenic effect
Transplanted Human Amniotic Epithelial Cells Secrete Paracrine Proangiogenic Cytokines in Rat Model of Myocardial Infarction.	Song et al.	Cell Transplant.	2015	Experimental	South Korea	Evaluate the paracrine effects in myocardial function and regeneration after MI	Analyzing the in vitro cytokine expression profile in hypoxic hAMC in comparison to injured myocardium	Rat	Injection of hAMC	Positive secretion of proangiogenic cytokines in vitro and in vivo
Epithelial-to-Mesenchymal Transition Enhances the Cardioprotective Capacity of Human Amniotic Epithelial Cells.	Roy et al.	Cell Transplant.	2015	Experimental	Germany	Augmentation of myocardial regeneration capacity in vitro and in vivo of amniotic epithelial cells forced to epithelial-to-mesenchymal transition	Differentiation, paracrine effects, MI size, LV function, and angiogenesis	Rat	Injection of hAMC	Enhanced cardioprotective effects of hAMC
Amniotic mesenchymal stem cells with robust chemotactic properties are effective in the treatment of a myocardial infarction model.	Kim et al.	Int J Cardiol.	2013	Experimental	South Korea	Investigate the chemotactic abilities of hAMC in cardiac function and regenerative angiogenesis	Paracrine effects, LV function, and angiogenesis	Rat	Injection of hAMC	Elevated angiogenic gene expression, high migration and adhesion potential, improvements in LV function and transdifferentiation

In vivo differentiation of human amniotic epithelial cells into cardiomyocyte-like cells and cell transplantation effect on myocardial infarction in rats: comparison with cord blood and adipose tissue-derived mesenchymal stem cells.	Fang et al.	Cell Transplant.	2012	Experimental	South Korea	Assess if hAMC could differentiate into cardiomyocytes in vivo and whether hAMC transplantation could decrease MI size and improve LV function in comparison to transplantation of cord blood-derived or adipose MSCs	Differentiation, infarction size, and LV function	Rat	Injection of hAMC	Positive differentiation into cardiomyocyte-like cells, decreased infarct size and improvement in LV function
Xenografted human amniotic membrane-derived mesenchymal stem cells are immunologically tolerated and transdifferentiated into cardiomyocytes.	Tsuji et al.	Circulation Res.	2010	Experimental	Japan	Determine whether hAMC could be an ideal allograftable stem cell source for cardiac regenerative medicine	Differentiation and immunologic tolerance	Rat	Injection of hAMC	Positive differentiation into cardiomyocytes and immunological tolerance
Naive rat amnion-derived cell transplantation improved left ventricular function and reduced myocardial scar of postinfarcted heart.	Fujimoto et al.	Cell Transplant.	2009	Experimental	EUA	Investigated whether untreated naive rat amniotic-membrane transplantation into the injured myocardium is beneficial as a cell-based cardiac repair strategy	Cardiac remodeling and functional recovery	Rat	Injection of rat amniotic membrane	Preserved cardiac function and reduced myocardial scar formation

hAMC-decellularized human amniotic membrane, LV-left ventricle, MSC-mesenchymal stem cell, MI-myocardial infarction, MRI-magnetic resonance imagin.

area and infarct zone, were used by Khorramirouz et al. to suggest the regenerative and differentiation process of hAMC [22]. In a chronic MI model, Gorjipour et al. showed some differentiation into cells expressing cardiomyocyte markers, but they did not acquire the contractile function required for mechanical activity of the myocardial tissue [24].

Discussion

Cell-based therapies have emerged as possible alternatives for cardiac repair after myocardial infarction. The first report of hAMC as a potential strategy in regenerative medicine is from 2005, when Miki et al. suggested hAMC as a potential source of stem cells. The authors demonstrated that in vivo surface markers of embryogenic stem cells and the presence of pluripotent stem cell-specific transcription factors isolated from human placenta increased the potential of hAMC to differentiate into all three germ layers: endoderm, mesoderm, and ectoderm [7].

Since then, hAMC has been used as a potential therapeutic agent in different medical specialties, such as ophthalmology and surgery [26-28]. More recently, the application of hAMC in the infarcted heart has surfaced as a possible treatment for MI, based on not only the transdifferentiation theory, but also its anti-inflammatory, bacteriostatic, and anti-microbial properties [29, 30].

Experimental models have extensively analyzed changes in LV function following MI in rats. In general, ventricular function has been assessed by two-dimensional echocardiography with two different modalities: Simpson's volumetric and Teichholz volumetric assumption formula. Pressure-volume curves and MRI have also been described as possible techniques for estimating LV function. Most of the studies in the acute scenario have described a statistically significant improvement in LV function, with values as high as 15-20% augmentation in EF after therapy [14, 19, 21, 22, 24, 25].

Although results seem to be promising, the main limitations of the available data are the different techniques for estimating LV function as well as the small sample size of the studies. In addition, the somewhat promising results of the acute setting have not been replicated in the chronic scenario, where cell differentiation has been described but ventricular contractility has shown disappointing results. The infarcted area has also been assessed by different techniques, including Masson's trichome staining and immunohistochemistry. Similar to LV function, results vary across the different analyses, and conclusions on the real benefits of hAMC are difficult to reach [14-16, 18].

Differentiation into cardiomyocyte and neoangiogenesis are two suggested mechanisms by which hAMC may improve LV remodeling following MI [14, 15, 19, 21-23]. The potential of hAMC differentiation into cardiomyocyte has been widely studied in vivo and in vitro. Several studies, using different techniques, have proven the pluripotential capacity of hAMC; however, the main question remains on whether this differentiation could induce and improve myocardial contractility.

A study showing cardiomyocyte differentiation without contractile improvement in a chronic MI model raises the possibility that the main benefit of hAMC in MI may be related to its anti-inflammatory proprieties rather than an effective myocyte formation [24]. Unlike cardiomyocyte differentiation, neo-angiogenesis does not show strong evidence of improvement, with contradictory results mainly due to the different techniques used for assessing angiogenesis in the experiments.

In conclusion, hAMC may be a potential, costless alternative cell-based therapy for MI, being a possible source of stem cells with a tridimensional patch and anti-inflammatory proprieties. Improvements in LV function, LV remodeling and cardiomyocyte differentiation have been evidenced, though more homogeneous and larger studies are needed in the future.

Disclosure of conflict of interest

None.

Address correspondence to: Gustavo Gavazzoni Blume, Division of Cardiovascular Diseases, Catholic University of Paraná, Rua Imaculada Conceição, 1155, Prado Velho, Curitiba, Paraná, Brasil. CEP: 80215-901. Tel: 55-41-99979-9851; 55-41-3320-3500; E-mail: gustavoblume@gmail.com

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