Journal of Molecular and Cellular Cardiology 53 (2012) 899–905

Contents lists available at SciVerse ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Original article

Reduced CD26 expression is associated with improved cardiac function after acute myocardial infarction
Insights from the REPERATOR study

Simone Post [a,b,c,*], Alexandra J. van den Broek [a], Benno J. Rensing [b], Gerard Pasterkamp [a,c], Marie-José Goumans [a,d], Pieter A. Doevendans [a,c]

[a] University Medical Center, Division Heart & Lungs, Laboratory Experimental Cardiology, G02-523, Postbus 85500, 3508 GA Utrecht, The Netherlands
[b] Department of Cardiology, St. Antonius Hospital, Postbus 2500, 3430 EM Nieuwegein, The Netherlands
[c] Interuniversity Cardiology Institute of the Netherlands (ICIN), Postbus 19258, 3501 DG Utrecht, The Netherlands
[d] Leiden University Medical Center, Department of Molecular Cell Biology, Postbus 9600, 2300 RC Leiden, The Netherlands

ARTICLE INFO

Article history:
Received 7 August 2012
Accepted 31 August 2012
Available online 9 September 2012

Keywords:
Myocardial infarction
Homing
Blood cells
Magnetic resonance imaging
Remodeling
CD26

ABSTRACT

Peripheral blood mononuclear cells (MNC) enhance cardiac recovery and repair after myocardial infarction (MI). The SDF-1α/CXCR4 axis plays a major role in cell homing to infarcted myocardium and is negatively regulated by CD26. Therefore, we studied the expression of CD26 during MI and its effects on cardiac function. Blood samples from forty-two patients who underwent a primary percutaneous coronary intervention (PCI) for a first ST-elevated MI were collected during primary PCI, 1 week and 3 months after MI. Soluble CD26 (sCD26) and membrane bound CD26 expression on MNCs (mncCD26) were determined. Left ventricular function and infarct size were measured within 1 day, 1 week and 3 months follow up by magnetic resonance imaging.

One week post MI, sCD26 was down regulated compared to baseline, while mncCD26 was higher at baseline and 1 week compared to 3 months. Increased mncCD26 expression at 1 week after MI was associated with decreased overall recovery of left ventricular function as measured by left ventricular end systolic volume index. Furthermore, the in vitro migration capacity of MNCs to SDF-1α was decreased 1 week post MI and the migration capacity to SDF-1α was negatively correlated with mncCD26 expression. CD26 inhibition with sitagliptin – a drug currently used in diabetic patients – resulted in improved in vitro migration capacities of MNCs.

In conclusion, our preliminary results suggest that high cellular CD26 expression decreases the migration of MNCs towards SDF-1α and high cellular CD26 expression negatively influences cardiac function post MI. Treating patients shortly post MI with sitagliptin to inhibit CD26 may therefore increase MNC homing to the infarct area and could improve cardiac recovery and repair.

1. Introduction

Myocardial infarction (MI) is the leading cause of death worldwide [1]. Despite the modern management of MI with for example beta-blockers, statins and percutaneous coronary intervention (PCI), MI still has a high morbidity due to heart failure and/or arrhythmia: the 1-month mortality is 4–9% [2,3]. New treatment modalities are needed to prevent post-MI adverse remodeling. Both bone marrow and peripheral blood mononuclear cells (MNCs) are currently tested in clinical studies where they are infused intracoronary following successful reperfusion in MI patients. These MNCs were shown to modestly improve cardiac recovery and repair [4–7]. The mechanism by which MNCs improve cardiac function is not fully understood, but homing of MNCs is an important feature to be able to integrate in the damaged myocardial wall. A key chemokine regulating directed cellular migration is stromal cell-derived factor-1α (SDF-1α or CXCL12) [8]. SDF-1α is upregulated in the ischemic myocardium shortly after MI, resulting in recruitment of cells expressing the SDF-1α receptor CXCR4 on their surface from the circulation into the ischemic area of the heart [9]. The SDF-1α/CXCR4 homing axis is negatively regulated by the peptidase CD26 (dipeptidylpeptidase IV (DPPIV)) which cleaves the amino-terminal dipeptide from SDF-1α, generating an inactive protein [10,11]. Recently we showed

Abbreviations: DPPV, dipeptidylpeptidase IV; LV, left ventricle; LVESVI, left ventricle end-systolic volume index; MI, myocardial infarction; MNC, mononuclear cell; mncCD26, membrane bound CD26 expression on MNCs; PEA, percentage enhanced area; PCI, percutaneous coronary intervention; SDF-1α, stromal cell-derived factor-1α; sCD26, soluble CD26.

* Corresponding author at: University Medical Center, Division Heart & Lungs, Laboratory Experimental Cardiology, G02-523, Postbus 85500, 3508 GA Utrecht, The Netherlands. Tel.: +31 88 755 7155; fax: +31 252 2693.

E-mail addresses: s.post@umcutrecht.nl (S. Post), alexandra.vd.broek@gmail.com (A.J. van den Broek), b.rensing@antoniusziekenhuis.nl (B.J. Rensing), gpasterk@umcutrecht.nl (G. Pasterkamp), M.J.Goumans@lumc.nl (M.-J. Goumans), p.doevendans@umcutrecht.nl (P.A. Doevendans).

0022-2828/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.yjmcc.2012.08.026

that the dysfunctional homing capacity of MNCs from patients with the vascular disease Hereditary Hemorrhagic Telangiectasia type 1 to the infarcted myocardium was related to increased CD26 levels [12,13].

Therefore, we hypothesize that in patients with MI, high CD26 expression is negatively associated with the homing capacity of MNCs to the infarcted area and a reduced preservation of cardiac function.

2. Materials and methods

2.1. Patient population and study design

Between March 2006 and November 2007 forty-two patients were analyzed in the REPERATOR trial (Prevention of REPERfusion Damage and Late Left Ventricular Remodeling With ATORvastatin Administered Before Reperfusion Therapy) [14]. Patients were included in the St. Antonius Hospital Nieuwegein and University Medical Center Utrecht, The Netherlands. The current study was performed as a sub-study of the REPERATOR study in all forty-two patients. All patients presented with a first acute ST-elevation-MI and were treated with primary PCI. At inclusion, patients were randomized to treatment with atorvastatin 80 mg or placebo once daily starting prior to primary PCI. From day eight after PCI all patients were treated with atorvastatin 80 mg once daily. This study revealed that pretreatment with atorvastatin did not result in an improved cardiac function or decreased myocardial infarction size [15].

Furthermore, we included ten patients with stable coronary artery disease. These patients were scheduled for coronary angiography or elective PCI and had documented coronary artery disease. The investigation was approved by the medical ethics committee of both hospitals and conforms to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients. The REPERATOR trial was registered at ClinicalTrials.gov under identification number NCT00286312.

2.2. Magnetic resonance imaging

Early and late left ventricular function and infarct size were assessed by MRI (1.5 T Philips®, Best, The Netherlands), at baseline (within 24 h after inclusion), at 7 days and 3 months after MI. Steady state free precession cine sequences and gadolinium-enhanced images were analyzed using a 12 segment, 6–20 slice model. One observer blinded for treatment from one of the study centers interpreted the MRI scans. Left ventricle end-systolic volume (LVESV), left ventricle end-diastolic volume (LVEDV), left ventricle ejection fraction (EF), cardiac output (CO), percentage enhanced area (PEA) and percentage transmural infarcted area were calculated.

2.3. Blood samples

Blood was drawn before PCI, at second and third MRI. Blood samples were collected in Potassium/EDTA tubes (Vacuette, Greiner Bio-One, The Netherlands). Plasma samples were frozen and stored at −80 °C. Peripheral blood MNCs were isolated by density gradient centrifugation using Ficoll Paque Plus (Amersham Biosciences, Sweden), according to the manufacturer's protocol.

2.4. Flow cytometry

Flow cytometric analysis was performed using 100 μL whole blood or $3*10^{E}5$ MNCs in PBS. Cells were stained according to the manufacturer's instructions using the following monoclonal mouse-anti-human antibody combination: anti-CD14-ECD (Immunotech, Coulter, France), anti-CD26-FITC (Serotec, UK) and anti-CXCR4-PE (BD Pharmingen, USA). Isotype-matched fluorochrome-conjugated antibodies were used as controls. After incubation, samples were washed and, in whole blood samples, red blood cells were lysed before measuring fluorescence on a flow cytometer (Cytomics FC500, Beckman Coulter, The Netherlands). The MNC cell fraction was determined by forward and sideward scatter patterns. Analysis was

Table 1
Patient characteristics.

	n = 42
Age, years	57.0 ± 13.5
Gender (male), n (%)	32 (76.2)
Body mass index, kg/m^2	27.2 ± 4.0
Laboratory parameters	
Cholesterol, mmol/L‡	4.38 ± 1.27
HDL-cholesterol, mmol/L‖	0.82 ± 0.36
LDL, mmol/L‖	2.90 ± 1.30
Triglycerides, mmol/L‖	1.15 ± 0.56
Glucose, mmol/L*	7.5 ± 4.5
Creatinin, μmol/L	80.5 ± 28.5
Hemoglobin, mmol/L	8.90 ± 1.05
Leucocytes, G/L	11.1 ± 4.2
Medications after myocardial infarction	
Thrombocyte coagulation inhibitors, n (%)	42 (100)
Statin, n (%)	42 (100)
ACE-inhibitors, n (%)‡	23 (54.8)
Beta-blockers, n (%)‡	36 (85.7)
Angiotensin-II-receptor antagonists, n (%)‡	3 (7.1)
Calcium antagonists, n (%)‡	4 (9.5)
Myocardial infarction	
Anterior infarction, n (%)	10 (23.8)
Total ischemic time, minutes	168 ± 151
Peak CK, U/L	1198 ± 1596
Risk factors	
Smoking/history of smoking, n (%)	32 (76.2)
Diabetes, n (%)	6 (14.3)
Hypertension, n (%)	16 (38.1)
Hypercholesterolemia, n (%)‡	10 (23.8)
Positive family history, n (%)	20 (47.6)

Data are presented as number (percentage) or medium ± IQR. * n = 36; ‡ n = 41; ‖n = 40; due to missing data. ACE = angiotensin converting enzyme.

Table 2
Cardiac function and infarction size.

	baseline	1 week after AMI	13 weeks after AMI
Cardiac function			
LVESVI, mL/m^2	27.6 ± 11.6	27.8 ± 11.3	25.1 ± 9.7
LVESV, mL	55.6 ± 24.3	55.6 ± 22.4	50.7 ± 19.9
LVEDV, mL	115.6 ± 31.2	122.5 ± 30.3	117.8 ± 30.4
EF, %	53.0 ± 11.2*	55.3 ± 10.9	57.9 ± 10.9
CO, L/min	4.22 ± 0.91	4.28 ± 1.10	4.11 ± 0.94
Infarction area			
PEA (%)	18.7 ± 12.4*§	15.0 ± 11.5	14.1 ± 10.3
Change, time after AMI			
	1 vs. 0 weeks	13 vs. 0 weeks	13 vs. 1 weeks
Cardiac function			
LVESVI, mL/m^2	0.11 ± 7.1	−3.0 ± 10.0	2.8 ± 9.1
LVESV, mL	−0.16 ± 14.4	−5.9 ± 20.1	5.3 ± 18.3
LVEDV, mL	6.7 ± 19.7	1.5 ± 26.5	4.9 ± 23.5
EF, %	2.4 ± 6.5	5.4 ± 7.4	−2.8 ± 7.6
CO, L/min	0.077 ± 0.94	−0.095 ± 0.78	0.20 ± 0.89
Infarction area			
PEA (%)	−3.0 ± 3.3	−5.2 ± 5.2	−2.0 ± 4.8

Overview of parameters and change of cardiac function and PEA measured by MRI. Data are presented as mean or percentage ± SD. *P = 0.001 baseline versus 13 weeks after AMI; §P = 0.001 baseline versus 1 week after AMI.
LVESVI = left ventricular end-systolic volume index; LVEDV = left ventricular end-diastolic volume; EF = ejection fraction CO = cardiac output; PEA = percentage enhanced area.