

After a myocardial infarction, eosinophils help to improve heart function

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ABSTRACT

Changes in blood eosinophil levels and eosinophil cationic proteins have been discovered in clinical research to be risk factors for human coronary heart disease. Following Myocardial Infarction (MI), we found an increase in blood or heart eosinophil counts in humans and animals, particularly in the infarct zone. Post-MI cardiac dysfunction, cell death, and fibrosis are exacerbated by genetic or inducible eosinophil depletion, which is accompanied with an immediate increase in heart and a chronic rise in splenic neutrophils and monocytes.

Mechanistic studies show that eosinophil IL4 and the cationic protein mEar1 play a role in preventing H₂O₂- and hypoxia-induced cardiomyocyte death in mice and humans, as well as TGF-induced cardiac fibroblast Smad2/3 activation and TNF-induced neutrophil adhesion on the heart endothelial cell monolayer. In vitro-cultured eosinophils from WT mice or recombinant mEar1 protein efficiently cure aggravated cardiac dysfunctions in eosinophil-deficient dblGATA mice, but not eosinophils from IL4-deficient animals. Eosinophils play a cardioprotective role in post-MI hearts, according to this study.

Key Words: Myocardial infarction; TNF-induced neutrophil

INTRODUCTION

The transcription factor GATA-1, as well as the cytokines IL3, IL5, and GM-CSF, govern the development of eosinophils (EOS) in the bone marrow. Major basic protein, eosinophilic cationic protein (ECP), eosinophilic peroxidase, cytokines (IL4, IL5, IL10, IL13), and chemokines are all found in the cytoplasm of EOS cells (CCL3, CCL5, CCL11). Activated EOS have long been thought to be hazardous effector cells that produce these granule components. EOS levels rise in the blood and accumulate in the tissues of people who have hypersensitivity or parasite infections [1]. Plasma ECP, a biomarker of EOS activation, is higher in patients with asthma and other atopic or inflammatory illnesses. EOS may also play a role in Coronary Artery Disease in humans (CAD). Patients with Acute Coronary Syndromes (ACS) or after Percutaneous Coronary Intervention (PCI) have a higher blood EOS count, which correlates with CAD prevalence and can be used as a biomarker for risk classification in these patients. Blood EOS increases for at least 5 days after a myocardial infarction (MI), while plasma ECP peaks within the first 2-3 days.

Plasma ECP is linked to coronary artery disease¹⁰ and a worse prognosis in PCI patients. EOS is seen in autopsy specimens from patients with instant stenosis and atherectomy specimens from patients with cardiac rupture after a MI.

Other research, on the other hand, imply that EOS may play a preventive effect in CAD. A low EOS count indicates cardiovascular death and has a negative correlation with death rates [2]. Over the course of 6 months of follow-up in the CALIBER study, a strong correlation was found between low EOS count and heart failure, unheralded coronary death, ventricular arrhythmia/sudden cardiac death, and subarachnoid haemorrhage in 775,231 people aged 30 or older who did not have CAD at baseline. A low EOS count was also associated with a lower risk of peripheral artery disease (HR: 0.63), albeit the link faded after 6 months. Increased EOS in peripheral blood and infarcted hearts after a MI may serve a compensatory and cardioprotective role in reducing cardiomyocyte death, cardiac fibroblast activation and fibrosis, and inflammatory cell adhesion and accumulation, according to this study [3].

RESULTS

Increased blood EOS counts in patients with previous acute MI

The Odense-based Danish Cardiovascular Screening Trial (DANCAVAS) is a randomised controlled trial including males aged 65 to 74 years old from southern Denmark. We randomly chose 5,864 men from the research who had blood samples obtained and blood EOS counts accessible.

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345 of them had suffered from a severe MI (AMI). High blood EOS counts were linked to BMI, current or past smokers, diabetes, ischemic heart disease, chronic obstructive pulmonary disease, usage of low-dose aspirin, statins, loop diuretics, and inhalation treatment. High blood EOS counts were determined to be a significant risk factor for human AMI after adjustment for possible confounders, according to multivariate logistic regression analysis. EOS counts were also strongly linked with BMI category, previous or present smoking, and usage of statins and low-dose aspirin, but data from COPD and diabetics revealed no relevance. The Eur-QoL-5D and NYHA classifications were positively linked with high blood EOS numbers. Lower mobility is linked to higher EOS counts. After correction, the relationship with the NYHA categorization group remained substantial [4].

Increased blood and myocardial EOS accumulation post-MI in mice

In mice, occlusion of the left anterior descending (LAD) coronary artery caused MI. The FACS gating technique to detect CD45⁺CD11b⁺ Siglec-F⁺CCR3⁺ EOS was established using single-cell preparations from 1-day post-MI mice's hearts. The FACS technique specificity was evaluated using sham-operated mice from wild-type (WT) and EOS-deficient *dblGATA* mice. Blood EOS counts increased one day after MI, just as they did in humans. The number of heart EOS cells per heart and their percentage relative to total heart CD45⁺ cells increased dramatically 13 days after MI, far more than in sham-operated animals. Over time, such a rise dwindled. The production of MI in *eoCRE*⁺/⁻*GFP*⁺/⁻ mice enabled for the detection of GFP-positive EOS in infarcted hearts [5]. GFP antibody immunofluorescent labelling one day after MI revealed EOS accumulation primarily in the infarcted region, with fewer on the border and very few in the remote region. EOS was also found in very little amounts in the hearts of sham-treated animals. The fact that cardiac EOS increased after a MI shows that the MI caused heart EOS adhesion and chemoattraction.

EOS deficiency exacerbates cardiac dysfunctions post-MI

We used sham and MI in 8-week-old male WT and *dblGATA* mice and assessed cardiac functions at 1-month post-MI to see if elevated heart and blood EOS after MI alter cardiac function and remodelling. MI generation lowered EF and FS, increased LV end-systolic (LV Vol_s) and end-diastolic (LV Vol_d) volumes, and raised the heart weight-to-body weight ratio (HW/BW) and heart weight-to-tibia length (HW/TL), as expected. Although the mortality rate was not differing between the groups, EOS deficiency in *dblGATA* mice did not ameliorate but worsened post-MI cardiac dysfunctions [6]. Following a MI, an increase in cardiac EOS may lead to an increase in EOS molecule synthesis. EOS produces the most of the Th2 cytokine IL4 in the heart, accounting for 65 percent of IL4 production in myocarditis-affected mice's hearts. Immunoblot analysis indicated a large increase in IL4 concentrations in the heart of WT mice 1 day and 1 month after MI, but a significant decrease in IL4 concentrations in *dblGATA* animals, indicating that EOS play a major role in IL4 synthesis in the heart after MI. mEar1 expression rose in 1-day post-MI hearts as well, however it was muted in *dblGATA* mice [7]. During the first week after a MI, there is a burst of acute inflammation. Within hours of commencement, neutrophils are the first innate immune cells to be attracted to the ischemic myocardium, and they gradually resolve by day three. Neutrophil influx into infarcted hearts is inhibited, which lowers infarct size and improves survival and cardiac function. At 1–3 days after MI, pro-inflammatory Ly6ChiCCR2⁺CXCR1lo (CD14⁺ in humans) monocytes predominate. Cardiac repair is improved by targeting Ly6Chi monocyte recruitment to reduce inflammation, but reparative Ly6CloCCR2⁻CXCR1hi (CD14dimCD16⁺ in humans) monocytes

produce VEGF and TGF- β , which stimulate angiogenesis, extracellular matrix protein synthesis, and myocardial healing.

Data showed that the neutrophil chemokines Cxcl1 and Cxcl3 were expressed much greater in *dblGATA* hearts than in WT hearts, however other chemokines (Cxcl2, Cxcl5, Cxcl7) did not reach statistical significance. Grew Ly6Chi monocytes in WT mice hearts increased even more in *dblGATA* hearts three days after MI, while the reparative Ly6Clo monocytes in *dblGATA* hearts remained blunted. Although the increase in cardiac monocytes was lower at 5 days after MI than at 3 days after MI, *dblGATA* hearts still contained more Ly6Chi monocytes than WT hearts, and *dblGATA* hearts had less Ly6Clo monocytes [8].

DISCUSSION

In ischemia-injured mouse hearts, this study shows that EOS has a cardioprotective effect. The same outcome was reached in both genetically EOS-deficient *dblGATA* mice and DTX-induced EOS-depleted *iPHIL* mice. While we found that patients with AMI have considerably higher blood EOS counts than those who do not have AMI, MI generation in mice likewise enhanced blood and cardiac EOS accumulation. The findings of this study back up the theory that an increase in heart and blood EOS after a MI is a compensatory strategy to protect the heart from ischemia harm. Although other mechanisms may be involved, this study found that EOS protects cardiomyocytes from H₂O₂ or hypoxia-induced cell death, which is one of the major events in ischemic hearts, reduces TGF-induced cardiac fibroblast Smad2/3 activation and collagen synthesis, which regulate cardiac function, and blocks the adhesion of neutrophils and possibly other untested inflammatory cells, which may reduce infiltration of these in the heart. Although blood ECP levels in acute MI patients peak within the first two weeks of the infarct, some researchers believe that ECP can increase endothelial adhesion molecule expression and enhance monocyte recruitment to the myocardium. Nonetheless, the current findings indicate mEar1's cardioprotective role in post-MI mouse hearts, which is consistent with previous research showing that ECP reduces T-cell responses to antigens, prevents immunoglobulin formation, and modifies fibroblast activity. Many other potentially significant EOS cytokines and cationic proteins, which may also have a role in decreasing post-MI cardiac cell death, fibrosis, and inflammatory cell recruitment, were not investigated in this study. Although our findings showed that mEar1, the human ECP ortholog, plays a direct function in decreasing heart ischemia-induced damage in all important cardiac cells tested (cardiomyocytes, cardiac fibroblasts, and MHECs), EOS cytokines may serve both direct and indirect effects. This study found that IL4 has a direct involvement in cardiomyocyte death reduction, as well as an indirect role in cardiac fibroblast fibrotic signalling through altering the expression of mEar1 and other untested molecules [9]. In ischemically wounded mouse hearts, EOS may still produce the majority of IL4. This notion is supported by observations such as the significantly lower increase in IL4 in *dblGATA* mice after MI. In this situation, however, Th2 and NKT cells in post-MI hearts may also contribute to IL4 production. This study did not test the notion that IL4 from these inflammatory cells has similar activities to IL4 from EOS in healing the heart from post-MI harm. First, as previously stated, we only have indirect evidence that EOS-derived IL4 plays a role in cardiac fibrosis by regulating EOS mEar1 expression, though IL4 did block H₂O₂-induced cardiomyocyte death, and EOS-deficient *dblGATA* mice had significantly lower heart IL4 levels at 1-day and 1-month post-MI. Other EOS cytokines might have a similar effect. Furthermore, each cytokine may have a distinct effect than the others. IL13^{-/-} EOS, for example, performed similarly to WT EOS in reducing neutrophil adherence on the MHEC monolayer and H₂O₂-induced cardiomyocyte mortality, as well as inhibiting Smad3

activation, but not Smad-2 activation. Second, the cardioprotective effects of EOS were only observed in male mice. Female mice with EOS deficiency showed no phenotypic differences from WT control mice after MI. We didn't test the mechanics behind these findings further, and we don't know if they hold true in humans. Because the DANCAVAS trial is only for men, our cohort will not be able to respond to this question. Third, as previously mentioned, dblGATA mice's spleens had lower amounts of Treg cells at 1-month post-MI when compared to WT control mice. In spleens from DTX-treated iPHIL mice compared to untreated control iPHIL mice, there was no such reduction [10]. Reduced splenic Treg cells in dblGATA mice may be related to alterations in other inflammatory cells caused by EOS deficit, rather than EOS deficiency itself, because EOS co-culture did not promote, but rather reduced Treg cell development. Fourth, compared to many other inflammatory cells, EOS accumulation in the heart after MI was comparatively minimal. There were roughly 3000 EOS per heart one day after the MI, far fewer than neutrophils, Ly6Chi, and Ly6Clo monocytes. Heart EOS counts had approached neutrophil levels three days after the MI, but only approximately a third of Ly6Chi monocytes remained. According to the findings, EOS in the heart after a MI affects the accumulation of other inflammatory cells.

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