Abstract: 42

Pericardial adipose tissue regulates granulopoiesis, fibrosis and cardiac function after myocardial infarction

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Topic(s):
Ischemia, Infarction, Cardioprotection

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S11

Background: The pericardial adipose tissue (AT) contains a high density of lymphoid clusters. Is unknown whether these clusters play a role in post-myocardial infarction (MI) inflammatory responses and cardiac outcome.

Methods: Lymphoid clusters were examined in epicardial AT of humans with or without coronary artery disease (CAD). Murine pericardial lymphoid clusters were visualized in mice subjected to coronary artery ligation. To study the relevance of pericardial clusters during inflammatory responses after MI, we surgically removed the pericardial AT, performed B cell depletion and GM-CSF blockade. Leukocytes in murine hearts, pericardial AT, spleen, mediastinal lymph nodes, and bone marrow were quantified by flow cytometry. Cannabinoid receptor CB2 (CB2/-/-) mice were used as a model for enhanced B cell responses. The effect of impaired dendritic cell (DC) trafficking on pericardial AT inflammatory responses was tested in CCR7-/- mice subjected to MI. Cardiac fibrosis and ventricular function were assessed by histology and echocardiography.

Results: We identified larger B cell clusters in epicardial AT of human CAD patients compared to controls without CAD. Infarcted mice also had larger pericardial clusters and 3-fold upregulated numbers of GM-CSF-producing B cells within pericardial AT, but not spleen or lymph nodes. This was associated with higher DC and T cell counts in pericardial AT, which outnumbered DCs and T cells in lymph nodes. Analysis of DC maturation markers, tracking experiments with fluorescently labelled cells and use of CCR7-deficient mice suggested that activated DCs migrate from infarcts into pericardial AT via CCR7. B cell depletion or GM-CSF neutralization inhibited DC and T cell expansion within pericardial AT, and translated into reduced bone marrow granulopoiesis and cardiac neutrophil infiltration 3 days after MI. The relevance of the pericardial AT in mediating all these effects was confirmed by removal of pericardial AT and ex vivo coculture with pericardial AT and granulocyte progenitors. Finally, enhanced fibrosis and worsened ejection fraction in CB2/-/- mice was limited by pericardial AT removal.

Conclusions: Our findings unveil a new mechanism by which the pericardial AT coordinates immune cell activation, granulopoiesis and outcome after MI.