THE ROLE OF VCAM-1/VLA-4 INTERACTION IN VIRUS-INDUCED DILATED CARDIOMYOPATHY

ACC Moderated Poster Contributions
McCormick Place South, Hall A
Monday, March 26, 2012, 9:30 a.m.-10:30 a.m.

Session Title: New Mechanisms from Experimental Models
Abstract Category: 15. Heart Failure: Basic
Presentation Number: 1219-281

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**Background:** Vascular cell adhesion molecule 1 (VCAM-1) is a chemoattractant known to be upregulated in inflammatory diseases resulting in migration of bone marrow-derived cells (BMCs) to the site of inflammation via interaction with its ligand VLA-4. Furthermore, VCAM-1 was found to be upregulated in explanted hearts with dilated cardiomyopathy (DCM). However, it is unknown if the VCAM-1/VLA-4 interaction has a positive or negative impact on the progression of the disease. Therefore, we aimed to analyze the role of VCAM-1/VLA-4 interaction in a murine model of virus-induced DCM.

**Methods and Results:** A screening of chemoattractants in mice with coxsackievirus B3 (CVB3) induced DCM by RT-PCR revealed that VCAM-1 was upregulated in the diseased hearts. ELISA and immunohistochemistry confirmed the upregulation of VCAM-1 in virus-induced DCM hearts. BMCs (CD45+CD34+VLA-4+ cells) and resident cardiac progenitor cells (CPCs: defined as CD45-CD34-c-kit+ and CD45-CD34-Sca-1+ cells) analyzed by flow cytometry were increased in peripheral blood and in the diseased hearts. Boosting mobilization of BMCs by application of granulocyte-colony stimulating factor (G-CSF) resulted in an increased migration of VLA-4+ BMCs to the diseased hearts and an enhanced number of resident CPCs. This effect could be completely inhibited by additional administration of a VCAM-1 antibody demonstrating the predominant role of VCAM-1/VLA-4 interaction for BMC migration in virus-induced DCM. To analyze if this interaction has a positive or negative impact on the progression of the disease, cardiac function was evaluated by cardiac MRI before G-CSF application and 4 weeks thereafter. MRI detected a significant improvement of cardiac function after boosting migration of VLA-4+ BMCs by G-CSF. This was associated with reduced myocardial fibrosis and decreased numbers of apoptotic cardiomyocytes, analyzed by histology.

**Conclusions:** This is the first study showing that in virus-induced DCM, VCAM-1/VLA-4 interaction is crucial for recruitment of circulating BMCs, which is associated with an increase of CPCs. Furthermore, we could demonstrate that this interaction plays a beneficial role in this disease.