Monocyte driven immune response in experimental aortic valve stenosis

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Introduction: Symptomatic aortic valve stenosis (AS) is a severe health care burden which can only be cured by valve replacement. The development of AS is a complex inflammatory process, involving monocytes, macrophages and dendritic cells. In order to elucidate the exact function of pro-inflammatory classical and non-classical monocytes in disease initiation processes we conducted a series of experiments in a model of murine AS.

Material/Methods: Severe AS was induced in 10-12 weeks old male C57BL6/J or CX3CR1-deficient mice by introducing a coronary spring wire into the left ventricle, which was pushed and rotated over the aortic valve under echocardiographic guidance. Sham mice underwent surgical intervention by inserting the wire into the left carotid artery. Immune cells in the aortic valve were analysed using flow cytometry and immunofluorescence microscopy.

Results: Ultrasound analysis after two weeks confirmed the development of AS. Transaortic peak velocity levels were significantly increased compared to sham operated C57BL6/J mice. Flow cytometry of explanted aortic valves showed a strong cellular immunoreaction in the valvular tissue. Especially the number of Ly6Clow macrophages was significantly increased compared to sham mice, whereas the number of inflammatory Ly6Chigh monocytes remained stable. Immunofluorescence microscopy confirmed Ly6Clow macrophage infiltration in the valve, in close proximity to the endothelial cells on the ventricular and the aortic side. The expression of CD11b and CX3CR1 was significantly increased on the surface of the valvular Ly6Clow monocytes following AS induction. Using CX3CR1 deficient mice, AS development, measured by the peak velocity over the aortic valve, was significantly reduced compared to C57BL6/J mice.

Conclusion: In this study we were able to show that Ly6Clow macrophages dominate the immune response in AS pathogenesis and that CX3CR1 driven monocyte recruitment is involved in AS progression.

Keywords : Aortic valve stenosis, macrophages, monocytes, CX3CR1
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