Regulation of MMP activity influences cardiac fibrosis and cardiac inflammation during viral myocarditis

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Background:
Myocarditis, also known as inflammatory cardiomyopathy, is a severe inflammation occurring within the myocardium and can lead to heart failure or cardiac arrest. The detailed pathomechanisms are still unknown. Therefore, we investigated the role of Matrix-Metalloproteinase (MMP) activity mainly regulated by its inhibitors during myocarditis. We aimed to compare mice lacking Matrix-Metalloproteinase (MMP-13) and mice lacking the endogenous tissue inhibitor of Matrix-metalloproteinases (TIMP-1) during the acute phases of viral myocarditis. Since the activity of MMPs is mainly regulated by their endogenous inhibitors (TIMPs) the balance between both may affect cardiac inflammation as well as deposition of extracellular matrix and consequently the cardiac function.

Material and Methods:
We infected C57BL/6j mice lacking either the enzyme MMP-13 or its endogenous inhibitor TIMP1 as well as their corresponding littermates with coxsackievirus B3 and determined the hemodynamic LV-function 7 as well as 28 days after infection. Subsequently, we analyzed viral burden and viral replication in the cardiac tissue as well as the expression of cytokines and matrix proteins. Furthermore, cardiac fibroblasts were infected with virus to investigate if the viral infection alone induces pro-fibrotic signaling.

Results:
Severe cardiac inflammation was determined and cardiac fibrosis was predominantly co-localized with inflammation during the acute phase of myocarditis. Reduced cardiac function was detected in MMP13 KO mice as well as in TIMP1 KO mice after CVB3 infection. Furthermore, we observed differences in expression of matrix proteins but also for chemokines mediating cardiac inflammation. MMPs are responsible for both, regulation of cardiac fibrosis and inflammation during viral myocarditis in B6 mice.

Conclusion:
During the acute phase of myocarditis, observed cardiac fibrosis was consistently co-localized with the foci of inflammation. The activity of MMPs influences cardiac fibrosis as well as cardiac inflammation and consequently cardiac function. CVB3 infection induces pro-fibrotic signaling but also pro-inflammatory chemokine expression inducing cardiac inflammation. Therefore, we compared cardiac fibrosis, inflammation and function in mice
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lacking the enzyme MMP13 or its endogenous inhibitor during the acute phase of myocarditis.