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Promotionsverfahren von **Frau M.Sc. Anne Hemmers**
Auslage der Dissertation und Gutachten sowie Termin der mündlichen Prüfung
Anlage: Einseitige Zusammenfassung der Dissertation

Sehr geehrte Damen und Herren,

in dem oben genannten Promotionsverfahren wird die Annahme der Dissertation

Immune cell infiltration triggers heart failure after induction of pressure overload in cardiac p38 MAPKα-deficient mice

von den Berichterstattenden Prof. Dr. A. Gödecke und Prof. Dr. J. Altschmied beantragt. Sie kann zusammen mit den Gutachten in der Zeit

vom 23.05.2024 bis 03.06.2024

eingesehen werden. Bitte wenden Sie sich zur Einsicht an das Promotionsbüro (promotionmnf@hhu.de).

Einsprüche gegen diese Dissertation können nur zwei Tage nach der vorgenannten Frist geltend gemacht werden. Erfolgt kein Einspruch, so gilt die Dissertation als angenommen (§ 7 Ziffer (5) PO).

Sofern die Dissertation angenommen wird, findet die mündliche Prüfung am

06.06.2024 um 10.30 Uhr

im **Raum 25.23.U1.25** statt. Als Prüferinnen bzw. Prüfer sind vorgesehen:
Prof. Dr. J. Haendeler, Prof. Dr. S. Prömel und Prof. Dr. T. Klein.

Die Öffentlichkeit ist bei der Befragung nicht zugelassen.

Mit freundlichen Grüßen
im Auftrag

Kurzfassung der Dissertation - Anne Hemmers

Heart failure (HF) is associated with systemic, sterile inflammation of the myocardium, characterized by the infiltration of immune cells. Although chronic inflammation is recognized as a major factor in the pathophysiology of HF, the current treatment for HF-patients does not specifically target immune cells. This thesis should advance our knowledge of how immune cells impair cardiac function in HF conditions and pave the way for potential therapeutics targeting immune cell infiltration.

To study the infiltration of immune cells in cardiac tissue and the progression of fibrosis, a mouse model was used. In mice with a cardiomyocyte-specific deletion of the p38 MAPKα gene (iCM-p38 KO), the induction of pressure overload (PO) via angiotensin II (AngII) results in energy depletion and strongly impaired heart function just within 48h, characterized by a low ejection fraction (EF) (KO 25.8 ± 10.1% vs. control 51.9 ± 14.2%). Interestingly, the HF condition was reversible, since cardiac function recovered after the end of the 48h AngII treatment. A prolongation of the AngII treatment to 7d, however, resulted in a sustained deterioration of cardiac function for at least 14d beyond AngII administration in iCM-p38 KO mice.

The course of immune cell infiltration demonstrated a particularly strong infiltration after 48h of AngII treatment and an almost complete disappearance of immune cells at later times, despite continuous AngII administration. Interestingly, neutrophils and pro-inflammatory monocytes massively infiltrated the cardiac tissue of iCM-p38 KO mice after 48h of AngII treatment. In contrast, dendritic cells mainly infiltrated the hearts of control mice. Furthermore, cardiac fibrosis was observed in iCM-p38 KO hearts 3 weeks after the induction of PO. This is indicated by increased extracellular matrix accumulation and an increased expression of fibrosis-related genes.

Two attempts have been made to save the iCM-p38 KO phenotype. The first attempt targeted the increased sympathetic stimulation under HF conditions via β-blocker administration. However, an improvement of cardiac function did not occur. In a second attempt, neutrophils were targeted since a particularly strong infiltration was measured in iCM-p38 KO hearts. A depletion of early infiltrating neutrophils by injection of a α-Ly6G antibody resulted in a significantly improved cardiac function (EF increased up to 41.4%). Additionally, these hearts showed reduced signs of cardiac fibrosis.

In conclusion, this thesis demonstrates the importance of early neutrophil infiltration in the progression of chronic heart failure and shows that a treatment targeting this infiltration represents possibilities for therapy of HF patients.