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15.04.2024

Promotionsverfahren von **Frau M.Sc. Sophia Reidel**
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

Modulation of Neutrophil Phenotype in Myocardial Infarction and Diabetes

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

vom 26.04.2024 bis 07.05.2024

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

13.05.2024 um 10:30 Uhr

im **Raum 25.22.U1.33** statt. Als Prüferinnen bzw. Prüfer sind vorgesehen:
Prof. Dr. J. Altschmied, Juniorprof. Dr. M. Kutsch und Prof. Dr. E. Lammert.

Die Öffentlichkeit ist bei der Befragung nicht zugelassen.

Mit freundlichen Grüßen
im Auftrag

Silke Krispin

Abstract

A common cause of death in the western world are cardiovascular diseases (Roth, Huffman et al. 2015). Acute myocardial infarction (AMI) causes a profound sterile inflammation, and neutrophils are the first cells to massively infiltrate the infarcted area. This inflammatory response critically influences outcome after myocardial infarction. Until recently, neutrophils were thought to play a detrimental role in ischaemic heart disease since they enhance inflammation and tissue damage. However, it was lately shown that neutrophils also play an essential role in cardiac remodelling and repair post-MI, thus can have beneficial effects on myocardial healing (Ma, Yabluchanskiy et al. 2016). Comparable to macrophages, at least two distinct phenotypes exist for neutrophils (Fridlender, Sun et al. 2009). Pro-inflammatory N1- neutrophils are contra productive in healing and scar formation after a myocardial infarction, whereas anti-inflammatory N2 neutrophils carry out reparative effects and are involved in the resolution of inflammation, angiogenesis and tissue remodelling (Ma, Yabluchanskiy et al. 2016) (Hasan, Luo et al. 2016). It is well known that Type 2 Diabetes Mellitus (T2DM) strongly predisposes to cardiovascular diseases and it was reported that obesity and the following development of hyperglycaemia and hyperlipidaemia, often leading to T2DM and metabolic syndrome, results in chronic inflammation (Lumeng, Bodzin et al. 2007, Lackey and Olefsky 2016).

The major goal of this work was to investigate the modulation of neutrophil polarization towards an anti-inflammatory phenotype and the functional differences in the subtypes of neutrophils in wildtype and hyperglycaemic mice and after MI. The first part of the thesis "Modulation of Neutrophil Phenotype in Myocardial Infarction and Diabetes" concentrates on the characterization of murine bone marrow neutrophils and their polarization *in vitro* in presence of cytokines in a time frame of four hours. It was found that Interferon-γ/Lipopolysaccharide (IFN-γ/LPS) treatment strongly stimulated activation of murine BM neutrophils and led to the induction of a pro-inflammatory neutrophil phenotype. It was as well demonstrated that IL-4 skews neutrophils *in vitro* towards a N2-like neutrophil phenotype. Further, it was shown that neutrophils of male mice were more prone to pro-inflammatory polarization than neutrophils of female mice. Additionally, it was assessed that IL-4 and LPS/IFN-γ induced polarization is dependent on the Jak/Stat signalling pathway. It was demonstrated that, to a large extent N1 polarization by LPS/IFN-γ is dependent on Jak1 activation, which induces phosphorylation and activation of Stat1. In contrast, N2 polarization is mainly dependent on Jak2 activation, which leads to activation and phosphorylation of Stat6. Further, the effect of IL-4 on different neutrophil functions was investigated. This analysis revealed, that IL-4 was able to significantly reduce the formation of NETs and substantially increase the phagocytic capacity of neutrophils. However, IL-4 treatment had no effect on migration and degranulation of neutrophils.

In a second part, the effect of anti-inflammatory IGF-1 on neutrophils in the context of myocardial infarction *in vivo* was investigated and it was shown that IGF-1 treatment suppressed the pro-inflammatory neutrophil phenotype three and seven days after myocardial infarction.

In a last part, the effect of hyperglycaemia on neutrophil phenotype and function was investigated. This analysis revealed that severe hyperglycaemia substantially altered neutrophil phenotype towards a more pro-inflammatory phenotype with upregulation of, amongst others, genes involved in Nfκb signalling. Hyperglycaemia also affected neutrophil functions, as phagocytic capacity was reduced and the formation of NETs was slightly increased.

Thus, this study indicates that neutrophils might have a beneficial effect on myocardial healing by polarizing towards an anti-inflammatory phenotype and that hyperglycaemia induces a more pro-inflammatory neutrophil phenotype.

Sophia Rödel