INVESTIGATION OF DRUG-INDUCED CARDIOTOXICITY IN PRECLINICAL MODELS: FOCUSING ON CARDIO-ONCOLOGY AND HIDDEN CARDIOTOXICITY

PhD thesis

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1. Introduction

Drug-induced cardiotoxicity may present in many forms, including heart failure, increased risk of atherosclerotic cardiovascular disease (ASCVD), myocardial infarction, or arrhythmias leading to sudden cardiac death. Distinction should be made between the cardiotoxic effects of oncological and non-oncological drugs: with oncological drugs, the cardiotoxic effects may be more common and related to their main mechanism of action, and may not be possible to uncouple from their anti-cancer effects. Cardiotoxicity of anti-cancer drugs is widespread, including classical chemotherapeutic agents and newer, targeted therapies as well.

Cancer immunotherapy, including immune checkpoint inhibitors (ICIs), has received widespread attention due to its breakthrough effect in the treatment of many cancer types. Immune checkpoint molecules, such as programmed cell death protein-1 (PD-1), are physiological regulators of immune activation. Inhibition of immune checkpoint molecules with monoclonal antibodies represents a novel and effective anti-cancer therapeutic approach, nevertheless, numerous cardiovascular adverse events have been reported with ICI therapy, including myocarditis, progression of ASCVD, and heart failure. **The mechanisms of ICI-induced cardiotoxicities, including heart failure, are incompletely understood, highlighting the need for mechanistic investigations of these effects to understand the patients at risk and develop potential cardioprotective strategies.**

On the other hand, with non-oncological drugs, the cardiotoxic adverse effects are less common, however, they are one of the leading causes of post-marketing drug withdrawals**.** Screening studies for cardiotoxic effects are mandatory during drug development, nevertheless, drugs with cardiovascular adverse effects may still gain clinical approval due to undetected cardiotoxicity in preclinical and clinical studies – a phenomenon termed "**hidden cardiotoxicity**". Hidden cardiotoxic effects of drugs may only manifest in the diseased hearts, e.g., during or after myocardial infarction, however, these conditions are currently not tested during drug development. Thus, **improved preclinical testing systems are needed to identify hidden cardiotoxic effects at the early phases of drug development to decrease the number of patients at risk for these adverse effects in clinical trials and after marketization, in clinical practice.**

Investigating the hidden cardiotoxic properties of drugs that are indicated for the treatment of cardiovascular risk factors is of paramount importance, as the treated population is inherently more vulnerable to cardiac events. Bempedoic acid is a novel, first-in-class lipid-lowering drug that has been approved for the treatment of hypercholesterolemia and reduction of cardiovascular events. However, it has not been investigated previously in models of ischemic heart disease, e.g., ischemia/reperfusion injury, thus, a mechanistic investigation for hidden cardiotoxic effects is warranted.

2. Objectives

In this PhD work, we aimed to investigate two emerging topics in the field of drug-induced cardiotoxicity:

(1) In our first study, we studied the mechanisms of anti-PD-1 immune checkpoint inhibitor-induced cardiotoxicity in a mouse model to find molecular targets for ameliorating adverse cardiovascular events.

(2) In our second study, we aimed to investigate the potential hidden cardiotoxic properties of the novel antihyperlipidemic drug, bempedoic acid, in a rat model of acute myocardial ischemia/reperfusion injury.

3. Methods

3.1. Preclinical model for ICI-induced cardiotoxicity

C57BL/6J mice were treated three times a week for either 2 or 4 weeks with a dose of 200 μg per mouse (n = 10 per group), whereas BALB/c mice were treated for three times a week for 2 weeks with a dose of 200 μg per mouse (n = 10 per group). In separate experiments, C57BL6/J mice were randomly assigned to isotype control, anti-PD-1, anti-CD4, or anti-IL17A-treated groups (200 μg per mouse, n = 10 per group). After the treatment period, cardiac function was evaluated by echocardiography. Tissue samples were collected from the hearts, thymus, and spleen of the animals. Histological analysis was performed, including haematoxylin and eosin staining for gross examination and Sirius red staining for fibrosis detection, whereas anti-CD3ε immunohistochemistry was used for the detection of $CD3^+$ T-cells. RNA isolation, quantitative reverse transcription-polymerase chain reaction (qRT-PCR), and bulk RNA sequencing were used for the analysis of gene expression in tissues.

3.2. Preclinical model for the investigation of the potential hidden cardiotoxicity of bempedoic acid

Male Wistar rats (ranging from 92 g to 150 g at the beginning of the treatment) were treated with bempedoic acid (30 mg/kg, n = 26) or its vehicle, 1% hydroxyethylcellulose (n = 61), once daily by oral gavage for 28 days. After 28 days of treatment, animals underwent echocardiography, as described previously, to determine the cardiac

function of animals after chronic bempedoic acid treatment. Following the echocardiography, surgical induction of cardiac ischemia and reperfusion (I/R) was performed by occlusion of the left anterior descending coronary artery (LAD) for 30 min, followed by 120 min of reperfusion, while in one group ischemic preconditioning (IPC) was performed by three cycles of 5 min I/R prior to the index ischemia, as a positive control for cardioprotective effects in preclinical studies. Animals were randomized into the following surgical groups: vehicle + I/R (n = 26), bempedoic acid + I/R (n = 26) and vehicle + IPC (n = 35). After 120 minutes of reperfusion, hearts were excised and perfused in Langendorff mode to remove blood from the tissue, LAD was re-occluded, and the area at risk (AAR) was negatively stained with Evans blue dye through the ascending aorta. For the assessment of viable myocardial tissue, 2 mm-thick slices were cut and incubated in 1% triphenyltetrazolium chloride (TTC). The slices were scanned and assessed via planimetry. Infarct size was expressed as the proportion of the AAR. The severity and duration of I/R-induced arrhythmias were analyzed according to the Lambeth conventions.

4. Results

4.1. Investigation of ICI-induced cardiotoxicity

4.1.1. Anti-PD-1 impairs cardiac function in C57BL/6J mice

Treatment with anti-PD-1 significantly decreased left ventricular ejection fraction, while left ventricular mass and left ventricular internal diameter at systole and diastole (LVIDs and LVIDd, respectively) were significantly increased compared with the isotype control-treated group. Diastolic function was assessed by the ratio of early diastolic filling (E, measured via pulsed-wave Doppler) and early diastolic mitral annular tissue velocity (e', measured via tissue Doppler), which correlates with the end-diastolic pressure of the left ventricle. E/e' was significantly increased after 4 weeks of anti-PD-1 treatment. Global longitudinal strain (GLS), a sensitive parameter of early cardiac dysfunction, was significantly decreased due to anti-PD1 treatment after 4 weeks of treatment.

4.1.2. Anti-PD-1 leads to transcriptomic changes in the heart

To investigate the underlying mechanisms of ICI-induced cardiac dysfunction, we characterized the transcriptomic changes occurring after anti-PD-1 treatment in the heart with bulk RNA sequencing. After 2 weeks of PD-1 inhibitor therapy, 538 genes were differentially expressed after multiple comparison corrections, compared to isotype control treatment. Of these, 266 were upregulated and 272 were downregulated. After 4 weeks of PD-1 inhibitor therapy, 55 genes were differentially

expressed, with 17 being upregulated and 38 downregulated.

Furthermore, to analyze the functional changes after PD-1 inhibition, we have performed Gene Ontology (GO) analysis. After 2 weeks of treatment, several GO terms related to cardiac contractile function were downregulated, while GO terms indicating metabolic changes were upregulated. After 4 weeks, upregulated genes with the highest fold enrichment were related to antigen presentation via major histocompatibility complex (MHC) molecules.

4.1.3. Anti-PD-1 leads to immune activation in the thymus

To investigate the potential pro-inflammatory effects of anti-PD-1 treatment in the development of cardiac dysfunction, we have measured the changes in inflammatory gene expression locally (in the heart) and remotely (in the thymus and spleen) via qRT-PCR. Anti-PD-1 treatment significantly increased the expression of *Il1b* in the heart after 2 weeks, while *Aif1* and *Cd163* - markers of different macrophage populations - were increased after 4 weeks of PD-1 inhibitor treatment. However, other cytokines, or cell-type-specific markers of inflammation were not affected significantly, including *Cd3e* expression. Furthermore, CD3ε immunohistochemistry did not show an increase in $CD3^+$ T cells in the myocardium. However, after anti-PD-1 treatment, we observed increased gene expression of pro-inflammatory cytokines in the thymus (*Il3, Il6, Il17a, Il17f, Il23*). Of these, *Il17a,* encoding interleukin-17A (IL-17A), showed the highest increase compared to the isotype control-treated group. Importantly, gene expression of the anti-inflammatory cytokine

Il10 did not change significantly, leading to an increased *Il17a*/*Il10* ratio after anti-PD-1 treatment. Furthermore, we also assessed inflammatory changes in the spleen, where only *Ifng* showed increased expression after 2 weeks of anti-PD-1 treatment.

Altogether, these findings indicate that cardiac dysfunction after anti-PD-1 treatment in healthy C57BL/6J mice can develop independently of significant T-cell infiltration into the myocardium. However, gene expression of pro-inflammatory cytokines is markedly increased in the thymus, suggesting thymus alterations and remote cytokine production as a potential mediator of ICI-induced cardiac dysfunction.

4.1.4. Anti-PD-1 does not lead to cardiac dysfunction in BALB/c mice and leads to a more balanced cytokine response in the thymus

Following the findings that anti-PD-1 treatment induced pro-inflammatory gene expression in the thymus, we investigated the effects of PD-1 inhibition in BALB/c mice, a mouse strain known to differ in systemic T-cell-mediated immune response, mainly exhibiting a Th2-type immune response. In contrast to C57BL/6J mice, BALB/c mice did not show increased heart weight, left ventricular dilation, or cardiac dysfunction following PD-1 inhibition, suggesting that this strain of mice is resistant to anti-PD-1-induced cardiac dysfunction in this experimental setting. Moreover, we investigated inflammatory changes in BALB/c mice. In the heart, the expression of *Il4* and *Cd163* increased significantly, while in contrast to C57BL/6J mice, *Il1b* expression was

not altered. In the thymus, we have seen a prominent response to anti-PD-1 treatment, with the increase of *Il3*, *Il6*, *Il10*, *Il17a*, *Il17f*, *Il23*, *Rora*, and a decrease of *Il4* and *Gata3*. Interestingly, as opposed to C57BL/6J mice, the expression of anti-inflammatory cytokine *Il10* was significantly increased, leading to a lower ratio of *Il17a/Il10.*

4.1.5. Anti-IL17A treatment or CD4 T-cell depletion prevents the development of anti-PD-1-induced cardiac dysfunction

After the molecular characterization of ICI-induced cardiac dysfunction, we aimed to further investigate mechanisms that could be targeted pharmacologically to alleviate anti-PD-1-induced cardiotoxicity. Our previous results showed that the expression of several pro-inflammatory cytokines increased after anti-PD-1 treatment. Thus, first we aimed to deplete $CD4^+$ T cells, major contributors to cytokine production. As expression of *Il17a* was most prominently induced by PD-1 inhibition, we also targeted IL-17A with a monoclonal antibody, as a clinically relevant intervention. We have found that both depletion of $CD4^+$ T cells and selective blockade of IL-17A prevented the development of ICI-induced cardiac dysfunction, as shown by maintained EF in the respective groups, while EF was decreased with anti-PD-1 treatment alone.

4.2. Investigation of the potential hidden cardiotoxicity of bempedoic acid

4.2.1. Bempedoic acid pretreatment did not alter infarct size or mortality after ischemia/reperfusion injury

To investigate the potential hidden cardiotoxic effects of bempedoic acid, we have induced cardiac ischemia/reperfusion injury, as described previously. No statistically significant difference was found between groups in mortality during I/R surgery (I/R + vehicle: 19.23%, I/R + BA: 29.17%, IPC + BA: 10%, Chi-square test: n.s., n = 26–30/group). We measured myocardial infarct size, expressed as a proportion of the total LV area exposed to ischemia (area at risk, AAR). The AARs did not differ between groups (I/R + vehicle: 29.61% ± 3.08, I/R + BA: 33.90% ± 1.95, IPC + vehicle: 27.29% ± 2.30, Kruskal–Wallis test: n.s., n = 11-15/group). Chronic pretreatment with BA did not influence infarct size compared to the vehicle group, showing no hidden cardiotoxic (nor cardioprotective) effects, while the positive control for cardioprotective effects, IPC, significantly reduced it.

4.2.2. Bempedoic acid pretreatment decreased reperfusion-induced arrhythmias

Arrhythmias were analyzed by arrhythmia scoring, as described previously, and visualized using arrhythmia maps. The arrhythmia score during ischemia was not affected by bempedoic acid compared to the vehicle-treated group, while IPC significantly decreased it. However, during reperfusion, the arrhythmia score was significantly reduced both by bempedoic acid treatment and IPC, compared to the I/R + vehicle

group. The decrease in arrhythmia score during reperfusion by bempedoic acid can be attributed to the reduction in the incidence of non-sustained ventricular tachycardias (NSVTs). In summary, bempedoic did not show hidden cardiotoxic properties in terms of arrhythmia induction, in contrast, a mild decrease in reperfusion-induced arrhythmias was observed.

5. Conclusions

Here, we have shown that treatment with an anti-PD-1 immune checkpoint inhibitor monoclonal antibody induces cardiac dysfunction in C57BL/6J mice. This effect was associated with gene expression alterations in the myocardium and thymus. Whereas only mild inflammatory changes were seen in the heart, prominent upregulation of pro-inflammatory markers was observed in the thymus, especially in the case of IL-17A. These findings suggested the involvement of systemic immune activation after anti-PD-1 treatment in cardiac dysfunction development. Further investigating this, BALB/c mice (a strain with Th2-type immune response as opposed to Th1 in C57BL/6J mice) were treated with anti-PD-1, where cardiac dysfunction was not evident, and the gene expression in the thymus was more balanced between the upregulation of pro-inflammatory and anti-inflammatory cytokines. Lastly, we treated C57BL/6J mice with anti-PD-1 and neutralizing anti-IL17A antibodies, which successfully prevented cardiac dysfunction development, suggesting the potential role of IL-17A blockade in ameliorating anti-PD-1-induced cardiac dysfunction.

Moreover, we have tested bempedoic acid, a novel antihyperlipidemic drug, in a preclinical model of cardiac ischemia/reperfusion injury for potential hidden cardiotoxic properties. Here, we have found that bempedoic acid did not elicit hidden cardiotoxic effects in rats, while it reduced reperfusion-induced arrhythmias. These findings suggest that

bempedoic acid may be safely used during myocardial ischemia/reperfusion injury.

6. Bibliography of the candidate's publications

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