**Ruprecht-Karls-Universität Heidelberg**
**Medizinische Fakultät Mannheim**
**Dissertations-Kurzfassung**

# The role of Tiam1 in cardiac fibroblast activation

Autor: Jianyuan Pan
Institute: Institut für Experimentelle und Klinische Pharmakologie und Toxikologie
Klinik:
Doktorvater: Prof. Dr. T. Wieland

Abstract：Over the past decades, the contribution of non-cardiomyocytes such as cardiac fibroblasts to the development of heart failure have been widely studied. Different kinds of cardiac disease animal models are in use, with the most frequently pharmacological stress models being injections or perfusion of β-adrenoceptor (β-AR) agonist isoprenaline, and angiotensin II (AngII) perfusion to mimic hyperactivity of the sympathetic nervous system and/or the renin-angiotensin-aldosterone system (RAAS). In this study, the first aim was to investigate and validate the distinct contribution of α1-AR activation in cardiac remodeling on the background of β-AR stimulation during early hypertrophic growth by combining α1-agonist phenylephrine with isoprenaline (PE/ISO) and comparing this model to exclusive β-AR stimulation (ISO). Transcriptional analysis conducted in cardiac tissue at different time points during the first 7 days of perfusion revealed a transient, but prominent fibroblast activation which was more pronounced under ISO/PE than ISO-stimulation. However, subsequent analysis of a potential different RAAS activity by combining adrenergic perfusion with AngII receptor-1 antagonist losartan showed that both models relied on RAAS activation to normalize ISO-induced vasodilatation and to stabilize mean blood pressure indicating similar systemic AngII levels.
The second goal was to investigate the role Tiam1 in cardiac remodeling. Tiam1 has recently been shown to contribute to α1-AR-induced cardiomyocyte hypertrophy in vitro and its global depletion limited cardiac hypertrophy after ISO/PE challenge in vivo. After 4 days of ISO/PE perfusion, Tiam1 was upregulated in a similar pattern as the pro-fibrotic markers periostin and collagen1a1. Subsequent analysis of cardiomyocyte, fibroblast and endothelial cell enriched fractions showed that Tiam1 was exclusively upregulated in cardiac fibroblasts, but not in the two other cell types. Therefore, the study focused on the role of Tiam1 in cardiac fibroblast. The cells were challenged with ISO, AngII or endothelin-1 (ET-1) but remained unresponsive to α1-AR stimulation under the applied cell culture conditions. The data showed that pharmacological inhibition or depletion of Tiam1 reduced AngII, ET-1 and β2-AR/EPAC-mediated p38-phosphorylation, whereas p-ERK1/2 levels remained unchanged. In addition, Tiam1 inhibition and/or depletion reduced AngII-mediated YAP/TAZ activity, and proliferation. In conclusion, the results of this thesis indicated that chronic ISO/PE perfusion aggravates fibroblast activation compared to ISO alone. This aggravation appeared to be independent of RAAS hyperactivity in vivo, but in vitro experiment also did not support a presence of α1-ARs in cardiac fibroblast. During ISO/PE challenge the Rac1 activator Tiam1 was upregulated specifically in cardiac fibroblasts. In vitro analyses suggested a contribution of Tiam1 activity regarding canonical pro-fibrotic pathways in response to AngII, ET-1 and ISO stimulation.