Increased cardiovascular risk in patients with chronic kidney disease

Propositions accompanying the thesis

Increased cardiovascular risk in patients with chronic kidney disease: Insight into mechanisms and mediators of kidney-heart crosstalk

1. The knowledge generated in Chapter 3 on the increased levels of the drug metabolite MPA-G in CKD patients leading to cardiomyocyte dysfunction does not only warn to keep a good view on the dosage and MPA-G plasma concentration during treatment of CKD patients with mycophenolate mofetil, but may also lead to future studies aiming to improve the efficiency of MPA-G removal by dialysis and thus reduce its accumulation in CKD patients. (this thesis)

2. In an extended definition, this drug metabolite (MPA-G) could also be considered as an “exogenous uremic toxin”, since i) it was present in extended concentrations in blood and dialysate of CKD patients compared to non-CKD patients; and ii) this thesis could for the first time show adverse effects of MPA-G on cardiomyocytes in an in vitro study using concentrations found in CKD patients. (this thesis)

3. Interestingly, cardiomyocytes isolated from the remote area of hearts from patient with post MI heart failure have been shown to exhibit contractile dysfunction and disruption of calcium homeostasis [203]. Chapter 4 of this thesis extends this knowledge of impaired contractility in the remote area of infarcted hearts to the CKD context and identifies that in CKD context, S100A8/A9 and NR4A1 are interesting candidates for mediating worsened cardiac dysfunction post-MI. (this thesis)

4. Inflammation is a key player in cardiac remodeling post MI and timing of the inflammatory response is essential for proper regeneration post MI. Changes in cardiac remodeling post MI are accompanied by increased tissue damage as well as improper healing processes. (this thesis)

5. Current therapeutic options in patients with HF are largely on the basis of cardiovascular outcome trials, which assessed the effect of both medical and interventional therapy to reduce morbidity and mortality. However, patients with CKD have been excluded in most clinical HF studies, and recommendations for patients with CKD have to be extrapolated from subgroup analyses.

6. Therefore, better approaches for differentiating chronic hemodialysis patients at higher cardiovascular risk will help physicians improve clinical outcomes. Hence, there is an urgent need to discover feasible and reliable cardiac biomarkers to improve diagnostic accuracy, reflect myocardial injury, and identify high-risk patients.

7. Thus, in C57BL/6 mice, “multifactorial hit” models combining kidney injury and cardiovascular risk factors with high clinical relevance for patients with CKD, such as hypertension, seem to remodel pathophysiological processes in the heart better than “single hit” approaches.

8. Research is to see what everybody else has seen, and think what nobody has thought. (Albert Szent-Gyorgyi)

9. Who always does what he is already able to do, always remains what he already is. (Henry Ford)

10. When life gets you down, you know what you gotta do? Just keep swimming, swimming, swimming! (Dory, Finding Nemo, Disney)