DFG Forschergruppe 1054 (Research Group)

Sex-specific mechanisms in myocardial hypertrophy

Speaker
Prof. Dr. Vera Regitz-Zagrosek, Center for Gender in Medicine (GiM) and CCR
vera.regitz-zagrosek@Charité.de

Summary

Cardiovascular disease is the most common cause of death in men and women worldwide. Nevertheless, men develop most, but not all, cardiovascular diseases at an earlier age, while women have greater risks during invasive therapies. Heart failure (HF), a mal-adaptation to myocardial hypertrophy (MH), is a common cause of cardiovascular death. The adaptations in men and women are different. Understanding these differences could result in novel therapies that would benefit both men and women. The primary aim of this research is to investigate the protective effect of female sex in MH and HF. Female hearts develop a more favorable physiological form of myocardial remodeling when subjected to pressure or volume overload than male hearts. We hypothesize that the more favorable remodeling in female hearts involves the synergistic activity of several cellular-based protective pathways induced by estrogen signaling via estrogen receptors, thereby influencing mitochondrial function and myocardial energy metabolism. We speculate that in contrast, testosterone induces matrix remodeling and growth factor signaling via androgen receptors and contributes to eccentric remodeling, especially in males. We plan a series of inter-related mechanistic studies into sex differences in mitochondrial function, protein kinase B (AKT)-related signaling, fatty acid and arachidonic acid-related metabolism, and matrix synthesis. Animal models for physiological and pathological MH and HF, in combination with cell-specific and/or inducible genetic deletion or over-expression of hormone receptors, will be used to analyze hormone-related and chromosome-based sex differences. The role of estrogen and androgen receptors (ER and AR) and their interaction with hypertrophic signaling will be specifically analyzed. Simultaneously, we will compare stress-induced changes in the transcriptome and proteome in female and male myocardium to detect novel sex-specific pathways. We will test new pharmacological approaches for sex-specific effects. Finally, we will investigate whether or not the mechanisms observed in animal models can be applied to the human heart. A clinical study for sex differences in human aortic stenosis is associated with our project and will facilitate our hypotheses testing. Our research, albeit basic, could contribute directly to patient-oriented research by suggesting clinical protocols. In this way, we view our research as translational in nature.

List of projects and partners

List of projects and partners

Project	**Principal investigator (PI)**	**Project**
1.	V Regitz-Zagrosek S Mahmoodzadeh	ER modulation of myocardial energy metabolism contributes to sex differences in myocardial hypertrophy
2.	D Dragun V Gross	Sex differences in adaptive and maladaptive myocardial hypertrophy – role of the Akt/mTOR pathway
3.	M Bader	Role of androgens in the development of myocardial hypertrophy and heart failure
4.	O Huber	Estrogen and androgen-receptor crosstalk with β-catenin signaling and sex differences in myocardial hypertrophy
5.	J Klose	Sex differences in the cardiac proteome in response to physiologic and pathologic hypertrophy in animal models
6.	U Kintscher	The role of sex-specific lipolysis in exercise-induced cardiac hypertrophy
7.	W-H Schunck DN Müller	Sex-specific expression of cytochrome P450-dependent eicosanoids and their role in cardiac hypertrophy
Assoc. project	DFG Re 662/6-1 V Regitz-Zagrosek R Hetzer	Sex differences in human aortic stenosis