Cytokines and stress-induced myocardial hypertrophy and heart failure

Increased mechanical stress of the myocardium following hypertension and myocardial infarction induces release of hormonal factors, such as cytokines, which may induce myocardial hypertrophy and progression of heart failure. One goal of the work in our group is to identify cytokines that are regulated in heart failure, and to study those that promote myocardial hypertrophy and cardiac dysfunction. We have used microarray technology to identify regulated cytokines in hypertrophied and failing myocardium following myocardial infarction, and we have reported close to twenty cytokines that have never previously been assigned a role in heart failure. Using similar technologies, we have identified cytokines which are upregulated following aortic stenosis and pulmonary stenosis, and in models of cor pulmonale (hypoxia) and cardiomyopathy (conditional knock-out of the SR Ca\(^{2+}\) pump). The latter model, which was made in our institute, develops a severe diastolic dysfunction and has been thoroughly characterized at the organ and cellular level. Moreover, a patent on this mouse model has been published and currently the model is used by a number of scientists around the world. The regulated cytokines identified in the various models described above may actively contribute to the development and progression of heart failure through induction of hypertrophy and depression of cardiomyocyte contractility. One such example is the cytokine interleukin-18, which was found to be strongly upregulated both after myocardial infarction and in our cor pulmonale model. We have published data showing that interleukin-18 through its effects on phosphorylation of certain intracellular proteins may be importantly involved in development of diastolic dysfunction with possible therapeutic and diagnostic implications. Through our collaboration with the Research Institute for Internal Medicine and the Department of Cardiology at Oslo University Hospital Rikshospitalet (P. Aukrust, L. Gullestad), we have a unique opportunity to verify our findings obtained in...
experimental models by analyzing cytokine regulation in material from patients with different types of chronic heart failure. By this strategy we have identified activin A, leukemia inhibitory factor, interleukin-18 and fractalkine as novel possible mediators of heart failure development. We have also performed several studies showing that chemokines such as CXCL16, fractalkine and CXCL13 are increased in experimental and clinical heart failure, and identified an important role in extracellular matrix remodeling, especially by regulating a specific group of proteoglycans. Further studies will show how these cytokines directly affect disease progression in humans and whether they can act as targets for therapy or biomarkers of cardiac disease.

We have also identified a putative stress-sensor, syndecan-4, which may act in concert with cytokines, since it is a co-receptor for cytokines. The work was done in collaboration with researchers at Harvard University. An array of experiments has been performed showing that syndecan-4 interacts with calcineurin, which is considered to be one of the most important signaling molecules for myocardial hypertrophy. To ensure the relevance of the identified stress-sensor for human disease, we also analyze their regulation in patients.

Collaborations

Our group has collaborations with several world-leading institutions, but we also collaborate extensively within Center for Heart Failure Research which comprises thirteen groups in the Oslo region and in South-Eastern Norway Health Region. In collaboration with Department of Thoracic Surgery at Oslo University Hospital Ullevål (T. Tønnessen) we have studied the TGF-family of cytokines in patients with aortic stenosis and in mouse models of heart failure, and in collaboration with Department of Pulmonary diseases (O.H. Skjønsberg) we study the role of the innate immune system in lung diseases. Finally, in collaboration with Department of Cardiology at Akershus University Hospital (T. Omland/H. Røsjø) we have filed a patent on granins as biomarkers of cardiac disease based on studies in mice and humans.