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Therapeutic Designer Peptide to Combat Acute Heart Muscle Weakness

Researchers of the Heidelberg University, Heidelberg University Hospital (UKHD) and Heidelberg Institute for Theoretical Studies (HITS) have developed a synthetic peptide based on the natural protein S100A1, a nearly universal "fuel" for weakened hearts. The researchers combined computer-aided methods with lab studies to investigate the therapeutic effect of the so called S100A1ct peptide molecule. The results have been published in the journal "Circulation".

The protein S100A1 is produced in the heart muscle cells and an important controller of cardiac function: it regulates the pumping action of the heart, stabilizes the heart rhythm, ensures sufficient energy supply and effectively protects against maladaptive growth, for example after a heart attack, that normally leads to heart muscle weakness and heart failure. For a future therapeutic use of this protein, scientists from the Heidelberg Medical Faculty and the Faculties for Engineering Sciences and Bioscience of Heidelberg University developed a synthetic version of the protein by combining computer-based protein modeling and efficacy studies on heart muscle cells and animals. This approach led step by step to an optimized protein drug that could open up new treatment options for acute cardiac insufficiency.

The research group led by Dr. Julia Ritterhoff and Professor Dr. Patrick Most, Head of the Molecular and Translational Cardiology Section in the Department of Cardiology, Angiology and Pneumology at UKHD, has been studying the S100A1 protein for more than 20 years. The team has elucidated numerous functions of the protein in the cardiovascular system and, based on this work, has already developed gene therapy methods for the treatment of chronic heart failure. These approaches are now being prepared for clinical studies by a start-up company spun off from Heidelberg University and UKHD.

Part of the natural protein as an active agent against acute heart failure

Curiously, only a specific section of the protein seems to be responsible for the therapeutic effects of S100A1 in heart muscle. "This molecular insight gave rise to the idea of only using the putative active part of the S100A1 protein as a therapeutic agent." explains Dr. Ritterhoff. This short protein fragment, a so-called peptide, can be produced synthetically and directly applied intravenously as a drug with immediate therapeutic efficacy. Such a medicinal concept with precise regulation of the heart's contractile function via appropriate dosage would be conceivable, for example, in the context of intensive medical treatment of decompensated acute heart failure. In contrast the gene therapy is directed against chronic heart failure.

The development of this translational structure-based drug design concept was only made possible by the collaboration with the "Molecular and Cellular Modeling" group led by Professor Dr. Rebecca Wade at HITS and Center of Molecular Biology of Heidelberg University (ZMBH). The approach was to integrate experiments on heart muscle cells and animals and computational molecular modeling. "Our lab developed a customized computer-aided modeling pipeline for this project to model the molecular structure of the peptide and interactions with the predicted molecular effectors in the diseased heart cells. The computational modeling guided the design of specific experiments to investigate the molecular mechanisms. In this way, the strengths of computer-aided modeling and the experimental expertise of the lab of Dr. Ritterhoff and Prof. Most complemented each other very effectively" says Prof. Wade.

The peptide acts safely and therapeutically in clinically relevant preclinical models of heart failure

In their work, the two teams developed the basic structure of the new peptide, predicted its possible interactions with other proteins in heart muscle cells. They used various preclinical molecular, cellular and animal models to demonstrate that the new peptide therapeutic is safe and effective to reverse heart failure and that it even protects against lethal arrhythmias. "The special thing about the molecular mechanism of S100A1ct is, that it increases cardiac function of the weakened heart and at the same time protects against arrhythmias. The drugs currently available, which are used for acute decompensated heart failure treatment in intensive care, temporarily increase cardiac output but can have profound negative effects on the heart rhythm and worsen the prognosis of our patients", explains Prof. Most. "We therefore consider the S100A1ct peptide to be a real advance and particularly suitable for intravenous administration in the event of an acute drop in cardiac function, which

can occur following a severe heart attack or myocarditis, for example." Before it can be used in the clinic, however, preclinical development and safety assessments have to carried out.

The framework for the successful cooperation was provided by the Informatics for Life (I4L) Initiative, which was funded by the Klaus Tschira Foundation. The project received further financial support from the German Center for Cardiovascular Research with translational project funding from the Federal Ministry of Education and Research from the "Preclinical Confirmatory Studies" program. Cooperation partners were teams from the Center for Translational Medicine at Temple University, Philadelphia, USA, the cardiac surgery departments of the University of Pennsylvania, USA, and Essen University Hospital, as well as the Department of Clinical Pharmacology and Pharmacoepidemiology at the UKHD. The teams are now seeking collaborations with the biopharmaceutical industry in order to bring the peptide into clinical use.

Publication:
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