

Scientists find cause of fatal inflammation of the heart muscle

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Scientists of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), jointly with colleagues in the United States, have found out that inflammations of the heart muscle are caused by attacks of a specific type of immune cells. These immune cells attack the body's own tissue because during their maturation they did not have the chance to develop tolerance against a protein that is only found in the heart muscle.

An inflammation of the heart muscle, or <u>myocarditis</u>, frequently precedes a dangerous and often fatal heart enlargement. In many cases, the only promising treatment left is <u>heart transplantation</u>. For many years now, medical evidence has suggested that this dangerous inflammation is caused by autoimmune reactions, i.e., attacks by the body's own immune system.

However, it remained unclear whether it is antibodies or <u>immune cells</u> that damage the <u>heart muscle tissue</u>. It was also unknown which of the proteins in the <u>cardiac muscle</u> is the target of these fatal immune attacks. Jointly with colleagues from Harvard, the Dana Faber Cancer Institute and other U.S. research institutes, Professor Dr. Bruno Kyewski of the German Cancer Research Center (DKFZ) set out to investigate these questions.

The investigators studied mice that are often spontaneously affected by fatal myocarditis. Studying these animals, they discovered that α -MyHC, a type of heart muscle protein called myosin, is the target of



autoaggressive immune cells. This protein is highly specific of the heart muscle and is not found in muscles of the skeleton.

Why is it that immune cells suddenly start attacking a harmless own protein? "This is the result of a lack of tolerance training," says DKFZ's Professor Dr. Bruno Kyewski. T cells, a specific type of immune cells, are prepared for their job during their early development in a special organ called thymus gland. Here they are presented a multitude of the body's own molecules which they are expected to recognize as known and harmless on their later patrols through the body. "We have now discovered that there is no α -MyHC in the thymus tissue of these mice. T cells therefore have no opportunity during their 'education' to meet this protein and thus develop specific tolerance".

The scientists also provided proof of this hypothesis. They modified the mice's genetic material in such a way that their thymus gland became capable of producing α -MyHC. These animals were no longer affected by autoimmune myocarditis.

This hypothesis appears to be valid not only for mice, but also for humans. The investigators showed that human thymus tissue does not produce α -MyHC, either. Therefore, there are human T cells permanently circulating in the bloodstream which also have the potential of attacking the heart. "Normally, this causes no problems," said Bruno Kyewski. "But if the cardiac muscle gets damaged by a viral infection or an infarction and larger amounts of α -MyHC are released from the defective tissue, the fragile tolerance breaks down."

The results now published by the German-U.S. team are expected to contribute to developing more specific treatments against autoimmune myocarditis. So far, a common approach has been to attempt to suppress the production of antibodies in patients. "But now we know that we have to selectively block specific T cells to protect the heart in such cases,"



explained Kyewski.

More information: HuiJuan Lv, Evis Havari, Sheena Pinto, Raju V. Gottumukkala, Lizbeth Cornivelli, Khadir Raddassi, Takashi Matsui, Anthony Rosenzweig, Roderick T. Bronson, Ross Smith, Anne L. Fletcher, Shannon J. Turley, Kai Wucherpfennig, Bruno Kyewski and Myra A. Lipes. Impaired thymic tolerance to α -myosin directs autoimmunity to the heart in mice and humans. *Journal of Clinical Investigation*, 2011. DOI:10.1172/JCI44583

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