Proteasome inhibitor curbs severe myocarditis

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The outcome of viral myocarditis is closely associated with the immune response of the affected individual. An inhibitor of the immunoproteasome, a protein degradation complex in immunocompetent cells, reduces the extent of the inflammation and thus also the damage to the heart during myocarditis. Scientists of the German Centre for Cardiovascular Research (DZHK) and Charité – Universitätsmedizin Berlin have recently discovered this new treatment approach, as published in the scientific journal *EMBO Molecular Medicine*.

Viral infections of the myocardium can cause a devastating reaction of the immune system, which can lead to a severe inflammation with ensuing heart failure or even sudden cardiac death, especially in children and young adults. Activation of the immune response curbs the viral disease on the one hand, but causes pathological reactions in the myocardium on the other. The researchers are therefore attempting to identify new targets to weaken the immune response and simultaneously enable secure control of the virus. This is because the course of the disease appears to mainly depend on the interaction between the virus-mediated cell damage and the individual reaction of the body's own defence system. Thus, viral myocarditis is almost asymptomatic in most people.

Stable cardiac function

The DZHK scientist Professor Dr. Antje Beling of the Institute of Biochemistry at Charité–Universitätsmedizin Berlin and her team utilised an immunoproteasome-specific inhibitor, ONX 0914, with the aim of moderating severe courses of viral myocarditis. The immunoproteasome is a protease complex with various enzymatic activities that exists particularly in human immune cells where it degrades proteins. In an animal model with high susceptibility to severe viral myocarditis, this inhibitor could curb the destructive inflammatory reaction. Mice were infected with coxsackievirus B3, which also affects human cardiomyocytes, and were treated with the inhibitor ONX 0914 from the onset of the infection. Although the viral burden only sank fractionally with the inhibitor, less heart tissue was damaged and the cardiac function remained stable. "No severe inflammations that impair the filling of the myocardium and damage the myocardial tissue occur with the inhibitor. The heart can therefore pump unabated", explains Beling.

Inhibitor curbs cytokines

Monocytes and macrophages are those immunocompetent cells that substantially contribute to myocardial damage during a viral infection. For this reason, the Berlin based researchers investigated how these cells in infected animals reacted to the administration of the inhibitor. They observed that ONX 0914 indeed led to an increased mobilisation of monocytes from the bone marrow. However, these cells produced substantially fewer proinflammatory cytokines during the infection. Especially because of the low production of molecules that attract monocytes in the myocardium, no severe tissue-damaging inflammation could develop. "The inhibition of the production of proinflammatory cytokines is the main effect of the inhibitor ONX 0914, which leads to a better course of the myocarditis", says Beling.

In addition, the effect of ONX 0914 on other cells of the immune

system, such as lymphocytes and neutrophils, was analysed. During a viral infection, the scientists could observe in untreated mice that there was a sharp decline in the number of lymphocytes in the body, which was completely prevented by the treatment with ONX 0914. Similarly, they found more antibodies directed against the virus after administration of the inhibitor, which indicates that the immune system's antibody response remained intact or was even improved with ONX 0914. Neutrophil defence cells reacted clearly to the treatment with ONX 0914, yet it did not affect the course of the disease.

Great therapeutic potential

The researchers are currently trying to discover on a molecular level how the immunoproteasome-specific inhibition curbs the production of proinflammatory cytokines. They have already been able to ascertain that a particular cellular signal pathway, the so-called MAP kinase pathway, is involved in the effect's transmission. Moreover, Beling and her colleagues are examining in another myocarditis model whether ONX 0914 can develop the same protective effect there. "The active agent has great potential, not just for myocarditis, but also for other diseases which essentially arise from an exaggerated immune response", says Beling. An analogous inhibitor to ONX 0914 is already being tested in phase I/II clinical studies in patients with inflammatory autoimmune diseases.

More information: Nadine Althof et al. The immunoproteasome-specific inhibitor ONX 0914 reverses susceptibility to acute viral myocarditis, *EMBO Molecular Medicine* (2018). DOI: 10.15252/emmm.201708089

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