Eliminating cell receptor prevents infection in animal study

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New research from The Children's Hospital of Philadelphia sheds light on the role of cell receptors in acting as gatekeepers for infectious viruses. By using mice genetically engineered to lack a particular receptor in heart and pancreas cells, the study team prevented infection by a common virus that causes potentially serious diseases in humans.

"This finding is a step to understanding how cell receptors operate in infections," said study leader Jeffrey M. Bergelson, M.D., a pediatric infectious diseases specialist at The Children's Hospital of Philadelphia. "Scientists have identified receptors for many viruses that cause disease," said Bergelson, "but it is not always clear whether the receptors found in cell cultures actually play a role in the disease process. In this case, we confirmed that this receptor really is involved in the disease."

The current study, publishing July 23 in *Cell Host and Microbe*, focused on the coxsackievirus and adenovirus receptor (CAR), which Bergelson discovered in 1997. He previously found that, in cell culture, Group B coxsackieviruses (CVBs) manipulate cell signals to bind to the CAR.

CVBs are common in humans, usually causing minor, transient infections. However, this virus may at times cause potentially severe infections, such as myocarditis (in the heart) and viral meningitis (in the lining of the brain). CVB may also infect the pancreas, causing pancreatitis, and is suspected to contribute to childhood-onset diabetes.

Bergelson noted that his current animal study finding does not have

immediate implications for changes in patient care, although discoveries in basic biology often lay the foundation for future clinical treatments in unforeseen ways.

Viruses may have interactions in living organisms that differ greatly from their interactions in cell cultures. They may attack specific tissues in humans or animals, but without binding to the cellular receptors identified in cultured cells. For instance, adenovirus infects the liver, but it bypasses identified adenovirus receptors in that organ. Instead the virus engages in complicated interactions with blood proteins and unidentified molecules in the liver.

Therefore, Bergelson and colleagues set out to discover whether CVB interacts with its receptor to cause pancreatitis and myocarditis in a special breed of mice. By manipulating genes in the pancreas and heart that generate CAR in those organs, Bergelson's team prevented the mice from forming CAR at those sites. Subsequently, those mice had virus levels in the pancreas a thousand times smaller than in control animals, and had significantly less tissue damage and inflammation. A similar protective effect occurred in the mice designed to lack CAR in their heart cells.

The results indicate that CAR is the receptor used by coxsackieviruses to infect the heart and pancreas and to cause direct injury to tissues. In some patients, recovery from coxsackievirus infection is followed by slowly progressive inflammation and heart damage. Bergelson's lab is interested in whether this long-term damage also depends on virus interaction with CAR.

More information: Kallewaard et al, "Tissue-specific deletion of the coxsackievirus and adenovirus receptor (CAR) protects mice from virus-induced pancreatitis and myocarditis," *Cell Host and Microbe*, published July 23, 2009.

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