From blank round to a potently active substance?

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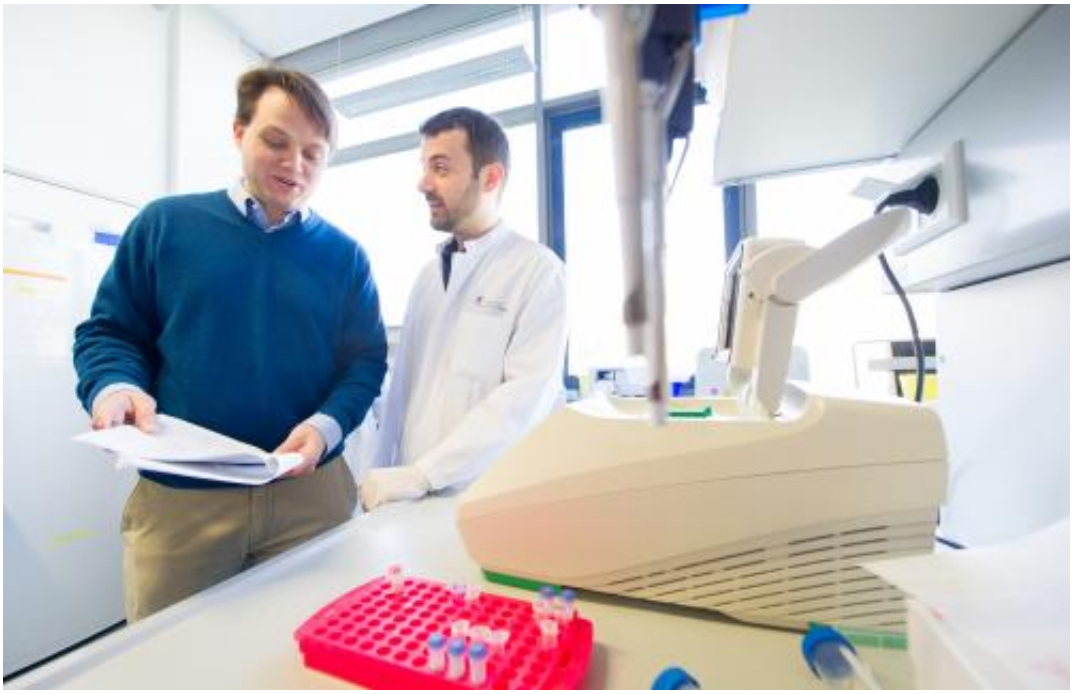

This is an image from the Institute for Clinical Chemistry and Clinical Pharmacology of the Bonn University Hospital. Credit: (c) Volker Lannert/Uni Bonn

A long-forgotten candidate for antiviral therapy is undergoing a renaissance: Since the 1970s, the small molecule CMA has been considered a potent agent against viral infections, yet it was never approved for clinical use. Scientists at the Bonn University Hospital have now deciphered how the molecule can actually stimulate the immune

system to combat viruses. The results are now being presented in the journal *EMBO* of the European Molecular Biology Organization.

Finding an active substance to stimulate the immune system and thus better combat dangerous viruses has been the dream of medical researchers for some time. Common viral diseases include influenza, hepatitis and AIDS. "A number of products have promised to activate the immune system but, in reality, there still is no such agent yet," says Prof. Dr. Veit Hornung from the Institute for Clinical Chemistry and Clinical Pharmacology of the Bonn University Hospital. The only substances that have been on the market to date prevent the proliferation of specific viruses, themselves. An active substance that could arm the immune system against a variety of viruses has not yet been discovered.

The compound CMA was only effective in mice and not in humans

At the end of the 1970s, scientists were nearing a breakthrough: 10-carboxymethyl-9-acridanone (CMA) appeared to be a suitable candidate for antiviral therapy. In the mouse model, CMA yielded unexpectedly potent activation of the immune system and a significant release of interferon resulting in an extremely strong antiviral effect. However, the result was unfortunately not reproducible in human cells. Why CMA stimulates the antiviral response in mice while showing no effect in humans has remained unexplained for quite sometime. That is until Prof. Hornung coincidentally saw an old publication regarding CMA and decided it was worthwhile to reexplore the mechanism of action of this molecule.

The same receptor - differing mechanism of action

Prof. Hornung believed that the lack of transferability between mice and

humans might be associated with the specific target structures that CMA latches on to. The team working with Prof. Hornung was then able to identify the protein to which CMA attaches, its receptor, in mouse cells. However, the human counterpart of this receptor did not respond to CMA. When CMA binds to the receptor in mice, a signal cascade is set into motion that leads to the release of interferons which in turn boost the immune system. However, in order for this to work, CMA and its receptor must fit together like a lock and key. Together with the laboratory of Prof. Dr. Karl-Peter Hopfner from the Gene Center at the Ludwig Maximilian University in Munich, the team from the Bonn University Hospital investigated the receptor variants of mice and humans in cell cultures and as purified proteins.

Animal models cannot easily be transferred to humans

"A few small differences in the receptor make the active substance completely ineffective in humans," reports lead author Taner Cavlar, postgraduate in Prof. Hornung's team. In humans, this prevents CMA from being able to latch its crucial receptor and release interferon, even though immune stimulation occurs in mice. "This is an example of the fact that results from animal models cannot always be easily transferred to humans," says Prof. Hornung. "Comparative investigations on human cells should take place at an early stage of active substance development."

Findings inspire the search for an antiviral drug

Since the scientists were able to figure out the exact structure of the mouse and human receptors, they now have an approach to see if there are conditions under which CMA could also arm the human immune system to fight viruses. This is now the next step which the researchers

want to address with their colleagues. However, it will likely take many years until an effective drug to combat viruses becomes available. "Nevertheless, when we are able to develop such a potent substance, only very small amounts would be enough to fight a variety of viral infections early on," says Prof. Hornung.

More information: Species-specific detection of the antiviral small-molecule compound CMA by STING, The *EMBO Journal*, DOI: 10.1038/emboj.2013.86

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