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Press Release

A 'finger' pointing the way to new hepatitis C medication

Braunschweig scientists develop compounds with potential against hepatitis C virus

Some 160 million men and women are infected with hepatitis C virus (HCV), the most common cause of cirrhosis and cancer of the liver. The present standard therapy is thraught with serious side-effects leading to a cure in only half of the patients. New therapies utilise small molecules that inhibit specific steps in the viral reproduction. However, the pathogen rapidly develops resistance, becoming insensitive to these agents. Researchers at the Helmholtz Centre for Infection Research (HZI) in Braunschweig, in collaboration with colleagues from the TWINCORE in Hannover have discovered new drug leads that are also efficient against resistant virus. They present their work in the "Journal of Biological Chemistry".

Interferons are used as classic medication against HCV as well as a few other viruses. Some interferons are produced naturally in the body in response to viral infection, others as immune modulators during inflammation. However, therapy with interferon is expensive, takes many months and has undesirable and unpleasant side effects. Hope was generated during the last few years through the development of a new generation of small drugs directed directly to the virus, in particular to those inhibiting the viral protease. These compounds inhibit viral replication by preventing the formation of the functional and structural components that must be cut out a precursor which the HCV virus instructs the host cell to produce in a single 'block'. This cutting, or processing, is initiated by the viral protease which mutates rapidly, generating resistant variants for which the protease-inhibitors have lost their effectivity.

Scientists from the group of Prof. John Collins at the HZI have succeeded in identifying novel small molecules that are active against HCV. "Our molecules use several sites of action in inhibiting the viral protease. Amongst these one which had not previously been addressed by existing protease inhibitors," explains Dr. Jonas Kügler, one of the participating scientists from the HZI. "Thus our molecules are effective against resistant virus with the expectation that the development of resistance will be more difficult," adds his colleague Dr. Stefan Schmelz from the group of Prof. Dirk Heinz. Kügler and Schmelz are the first authors on the publication. This work is a collaboration between the groups of Collins and Heinz and scientists from the TWINCORE , Hannover, in the institute of Prof. Thomas Pietschmann.

The development of the novel inhibitors used an approach which combined two different tactics: In one special iterative enrichment process using 'empirical selection', the scientists searched for small proteins that bound specifically to the desired target: the HCV protease. During the second step, suitable candidates were then slightly modified on the basis of 'rational design' and thus further optimized for the desired property. This resulted in molecules that have a strong inhibitory effect on the protease when added at a very low concentration. All of the molecules share a novel structural feature which the researchers call a 'tyrosine-finger'. This binds a region in the viral protease that was not bound by other inhibitors previously investigated.

“We do not expect that these molecules can be directly used for clinical antiviral therapy“ says John Collins. “Our results are, however, of great significance for the development of novel therapeutics effective even on virus resistant to other small inhibitors.” In the continuing race between the virus and the scientists, the researchers have achieved a new head-lead, or should one say a finger that points in the right direction.

Original publication:

Jonas Kügler, Stefan Schmelz, Juliane Gentzsch, Sibylle Haid, Erik Pollmann, Joop van den Heuvel, Raimo Franke, Thomas Pietschmann, Dirk W. Heinz and John Collins
High affinity peptide inhibitors of the hepatitis C virus NS3-4A protease refractory to common resistant mutants
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