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Press Release

HELMHOLTZ ZENTRUM FÜR INFEKTIONSFORSCHUNG

Direct access to desired genes

Study of natural compounds made simpler: Bacterial researchers develop improved DNA technique

Targeted exchange of DNA segments instead of tedious search: German and Chinese scientists have developed a technique for the direct isolation of genetic information from complex mixtures of different bacteria. Compounds produced by bacteria can often be used as pharmaceutics, for instance as antibiotics or chemotherapeutics. With the new method, they can be produced in the laboratory much easier than previously. The researchers describe this newly developed method in the journal Nature Biotechnology.

The method is a joint achievement of researchers from the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), a branch of the Helmholtz Centre for Infection Research (HZI) in Braunschweig, the Biotechnology Centre of the Technical University Dresden, the College of Life Sciences in Hunan/China and the company Gene Bridges in Heidelberg. Workgroups of Professors Rolf Müller, Francis Stewart and Youming Zhang were involved.

In addition to primary metabolism, which covers among other things the basic functions involved in housekeeping and reproduction, bacteria have also developed a number of secondary metabolic pathways. Products of these pathways are not essential for the survival of the bacteria, but help to improve adaptation to their environment. Many of these secondary metabolites are substances of pharmaceutical value. In order to characterize and analyze them for their potential medicinal application, researchers have to produce and isolate significant quantities of these compounds. Often it is difficult to harvest them from bacteria, as the exact conditions, under which the secondary metabolites are produced, are unknown. Thus scientists often isolate the genes, which are responsible for the production of the substance and transfer these to other bacteria that are easier to cultivate and produce the substance of interest.

To date, scientists have used a so-called DNA library for this task, which contains the whole genetic information of an organism as small pieces. After creation of a library, researchers had to screen it for the candidate gene. If a complete copy was present, they would transfer it to a special small DNA molecule and implant it into the target bacterium. There was an additional obstacle for natural compounds: “Often, a larger number of genes, so called gene clusters, are needed for the production of secondary metabolites. Their isolation is rather difficult”, explains Rolf Müller, director of HIPS and head of the department of Microbial Natural Products.

In the age of massive parallel DNA sequencing, the complete genomes of many bacteria are already known, and with them theoretically thousands of pathways for secondary metabolites. With the help of the newly described method of so-called “direct DNA cloning” genes for secondary metabolites can specifically be isolated and processed. The long detour via the DNA library can be bypassed.

To achieve this, participating scientists Xiaoying Bian of HIPS and Jun Fu from the Biotechnological Centre of the Technical University of Dresden and their colleagues have improved the patented technology of homologous recombination: Certain enzymes can be used to exchange a gene segment for a different, similarly composed segment. If the order of the components at the beginning and at the end of the gene of interest is known, a similar segment can be constructed and exchanged enzymatically. In principle, this method is not novel. However the enzymes currently used, Red-alpha and Red-beta, are not efficient enough to employ this approach for the isolation of large DNA segments and hence do not allow the subsequent production of natural compounds in the lab. The researchers have now discovered that certain variants of the enzymes RecE and RecT work much better than Red-alpha and Red-beta.

“Improved direct cloning makes it much simpler and shorter to isolate and characterize interesting secondary compounds” says Xiaoying Bian, one of the first authors of the study from HIPS. “The huge effort to create and screen a DNA library is now obsolete.” HIPS director Rolf Müller adds: “Many pathogenic bacteria have become resistant against common antibiotics and therefore it is crucial to find new substances to target infections. Our approach allows us to make use of the available complete genome sequences of many microorganisms for the targeted search for new compounds.”

The researchers have already employed the simplified method for the direct transfer of several gene clusters from the luminescent bacteria Photorhabdus luminescens to Escherichia coli. In doing so, they have identified two previously unknown secondary metabolites, Luminmycin A and Luminmide A/B.

Although this recently published study aims to illustrate the possibilities of the method, it also raises hopes for the discovery of novel natural compounds that can be used as antibiotics and thus lead to continued progress in fighting infectious diseases.

Original Publication:

Jun Fu, Xiaoying Bian, Shengbaio Hu, Hailong Wang, Fan Huang, Philipp M Seibert, Alberto Plaza, Liqiu Xia, Rolf Müller, A Francis Stewart & Youming Zhang (2012) Full-length RecE enhances linear-linear homologous recombination and facilitates direct cloning and bioprospecting, Nature Biotechnology, 30, 440-446.

The Helmholtz Centre for Infection Research (HZI):

The Helmholtz Centre for Infection Research contributes to the achievement of the goals of the Helmholtz Association of German Research Centres and to the successful implementation of the research strategy of the German Federal Government. The goal is to meet the challenges in infection research and make a contribution to public health with new strategies for the prevention and therapy of infectious diseases.
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