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1225 August 03rd, 2012

Press Release

Natural substances halt bacterial growth

US scientists explain mechanism of action of substances discovered at HZI

The current issue of the renowned scientific journal Science features the story of an international team of researchers and their serendipitous discovery of a group of natural substances capable of limiting bacterial growth. The substances – first described at the Helmholtz Centre for Infection Research (HZI) in Braunschweig, Germany – are inhibitors of RNA polymerase, the enzyme in charge of gene transcription in bacterial cells. Now, using highly sensitive analytic tools, scientists were at last able to demonstrate that these bioactive substances interfere specifically with the process of transcription by attaching to a site on the enzyme that is different from where traditional antibiotics normally attach – a property, which makes them very promising candidates in new drug design.

Myxopyronin, corallopyronin, and ripostatin are all different substances produced by a group of bacteria called myxobacteria. These microorganisms, which live in the soil, synthesize a number of biologically active chemicals. The antineoplastic properties of some of these chemicals, like epothilon, which was first discovered at HZI, make them effective agents in the fight against tumor cells – a property that has since been exploited in anti-cancer drug design. Others, like myxopyronin, corallopyronin, and ripostatin, are capable of killing off different types of pathogenic bacteria.

A number of years ago, HZI scientists had already begun to understand that these substances work by taking bacterial RNA polymerase out of commission. The specifics of this process have now been characterized as part of a collaborative research effort with Rutgers University in New Jersey, USA. It appears that the enzyme's basic molecular shape resembles that of a crab's claw. To attach the bacterial DNA, this "claw" must first be opened; once transcription has concluded, it closes up again. Myxopyronin, corallopyronin, and ripostatin all interfere with the opening of the enzymatic "claws," such that RNA polymerase essentially gets "stuck," remains closed, and is thus no longer capable of gene transcription.

Using the highly sensitive marker method "smFRET" – the acronym stands for "single molecule fluorescence resonance energy transfer" –, the US team, led by Richard Ebright and Anirban Chakraborty, was able to describe the exact distance between the two "tips" of the molecule's "claw" during different stages of the transcriptional process, which has helped them elucidate the substances' mechanism of action.

"What makes our substances so remarkable is that they work differently from other, known antibiotics," explains HZI scientist Dr. Rolf Jansen of the Microbial Drugs Department. "Their application in the fight against those bacteria that have evolved resistance to traditional antibiotics opens up a world of possibilities in terms of new drug design."

Adds Jansen's colleague, Dr. Herbert Irschik: "The substances cannot in their current form be used as drugs quite yet. True – they have proven highly effective against bacteria in vitro. However, before their full effect on the human body can be characterized and their tolerance with patients determined, we have to first continue to fine-tune their integration

into potential new drugs. At this point, it is too soon to say with certainty whether this will even be possible." Looking into this more is high up on the scientists' to-do list.

"Our findings point to myxobacteria's considerable potential vis-à-vis new drug design, and that of similar microorganismal natural substance producers," adds Prof. Rolf Müller, head of HZI's Department of Microbial Natural Products. "A number of drugs, most commonly those used in the fight against infectious diseases, are nature-made. We are quite certain that we will discover a number of equally promising natural substances over the next few years."

HZI's Microbial Drugs Department is concerned with the investigation of microorganismally produced substances that can be medically exploited, such as for use as antibiotics. The team's primary focus is on a group of bacteria called myxobacteria.

Original Publication:

Opening and Closing of the Bacterial RNA Polymerase Clamp Anirban Chakraborty, Dongye Wang, Yon W. Ebright, You Korlann, Ekaterine Kortkhonjia, Taiho Kim, Saikat Chowdhury, Sivaramesh Wigneshweraraj, Herbert Irschik, Rolf Jansen, B. Tracy Nixon, Jennifer Knight, Shimon Weiss, and Richard H. Ebright Science 3 August 2012: 591-595.

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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