Record reaction cascade yields cancer drug candidate

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(PhysOrg.com) -- New active substances can be produced quickly and efficiently with the help of reaction cascades. Once set in motion, these processes lead to the desired end product via a series of intermediate steps which take place in one go in a single reaction vessel. Scientists at the Max Planck Institute of Molecular Physiology in Dortmund have achieved a new world record in cascade synthesis: they succeeded in synthesising complex biologically active substances, Centrocountins, in twelve successive steps. These substances inhibit cell division and could provide new options for the development of antitumour drugs.

The organic synthesis of complex molecules is often laborious and time-consuming. To produce such molecules, chemists usually have to carry out numerous individual processes in sequence and isolate the intermediate products each time until they finally obtain the desired end product. In contrast, reaction cascades lead to the end product considerably faster: because they involve a kind of domino effect, it is sufficient to provide the starting materials and initiate the first step to reach the end product via a series of successive intermediate products and steps. Because the entire cascade takes place in a single reaction vessel, the isolation of intermediate products is dispensed with and the process saves time, energy and costs.

A team of scientists working with Herbert Waldmann, Director at the Max Planck Institute of Molecular Physiology in Dortmund has now succeeded in developing the longest reaction cascade known up to now. The researchers used it to synthesise biologically active substances

termed Centrocountins in twelve individual steps: Centrocountins are complex molecules which intervene in cell division and prompt tumour cells to commit cellular suicide.

“This process holds the current world record for cascade length,” says Kamal Kumar, a scientist at the Max Planck Institute in Dortmund who made a decisive contribution to the development of the synthesis process. The reaction begins with simple tryptamine derivatives and incorporates nine different individual reactions over twelve steps, which involve the use of two different catalytic mechanisms. The end products have a complex molecular structure with four ring systems. The entire reaction takes between ten and 30 minutes. “The production of molecules of this complexity using traditional methods would take days if not weeks,” says Kamal Kumar.

As tests on cell cultures showed, cells treated with Centrocountins did not divide in two but in three or more daughter cells which were not viable. The effect is due to the fact that the substances bind to certain proteins – nucleophosmin (NPM) and Crm1 – which play an important role in the formation of the spindle apparatus and organelles known as centrosomes, which provide starting points for the spindle apparatus. These structures ensure the correct separation of the chromosomes between the two daughter cells during cell division. As a result of treatment with Centrocountins, a dividing cell has multiple spindles poles instead of two. –. As a result, the cell can no longer correctly count its centrosomes – hence the name “Centrocountin”. The chromosomes are unable to orient themselves correctly at the metaphase plate and the cell division cycle comes to a standstill. The cell can only divide when all chromosomes are correctly arranged. The daughter cells produced in this way are not viable.

Due to their central role in cell division, the two proteins NPM and Crm1 are identified as potential molecular targets for cancer treatment.

“An active substance that binds to both NPM and Crm1 has not been available up to now,” says Slava Ziegler, a scientist at the Max Planck Institute in Dortmund who played a leading role in the identification of the target proteins. Hence, the new Centrocountins provide a promising starting point for the development of new tumour therapies.

More information: Heiko Dückert, Verena Pries, Vivek Khedkar, Sascha Menninger, Hanna Bruss, Alexander W. Bird, Zoltan Maliga, Andreas Brockmeyer, Petra Janning, Anthony Hyman, Stefan Grimme, Markus Schürmann, Hans Preut, Katja Hübel, Slava Ziegler, Kamal Kumar und Herbert Waldmann, Natural Product-Inspired Cascade Synthesis Yields Modulators of Centrosome Integrity, *Nature Chemical Biology*.

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