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How the bioweapon ricin kills - scientists solve mystery through revolutionary new technology

A key protein that controls how the deadly plant poison and bioweapon ricin kills, has finally been identified by researchers at the Institute of Molecular Biotechnology in Vienna, Austria. The discovery was made using a revolutionary technology that combines stem cell biology and modern screening methods, and reported today (Friday 2 December 2011) in the scientific journal Cell Stem Cell.

Shocking news spread in August this year. Al Quaida, a terror organization, was reported to be producing bombs containing the poison ricin to attack shopping centers, airports, or train stations. Since the First World War, ricin has had a gruesome reputation as a bioweapon. It is one of the deadliest plant based poisons in the world. Even a tiny amount can kill a person within two to three days after getting into the bloodstream. And it comes from the humble castor oil bean, available in many health food shops or online.

How the poison works

Castor oil is a powerful laxative, used medicinally for centuries, but the raw beans also contain small amounts of the poison ricin. So far no antidote is available. But now Ulrich Elling, a scientist on the research team led by Prof Josef Penninger at the Institute for Molecular Biotechnology (IMBA) of the Austrian Academy of Sciences in Vienna, has identified a protein molecule called Gpr107. This protein in the targeted cells is essential for the deadly effect of ricin. In other words, cells which lack Gpr107 are immune to the poison.

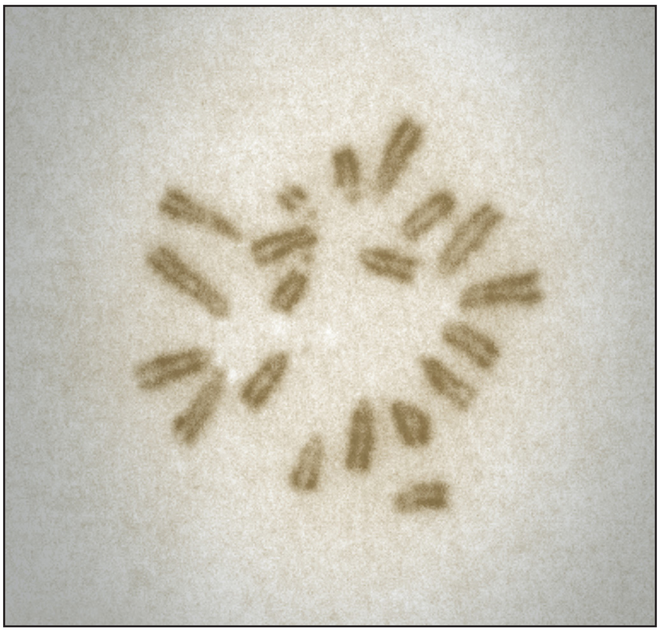
Ulrich Elling is optimistic, saying „Our research suggests that a specific antidote could now be developed by making a small molecule to block the Gpr107 protein."

New technology allows screening of the entire mammal genome

The researchers at IMBA were able to find in just a few weeks what others have been trying to find for decades. Their rapid success was made possible by a pioneering new method of genetic research developed largely by Ulrich Elling and Josef Penninger. With this new method, an entire mammal genome can be screened for mutations within a reasonable time frame.

Until now, screening methods for mice, rats and other mammals have focused on finding one single mutation. This was done using a technique called RNA interference or by breeding a suitable 'knock-out mouse' to study the effect of removing a single gene. But RNA interference doesn't always work, and breeding a knock-out mouse takes years and considerable effort.

That's why Josef Penninger sees this powerful technology as a revolution in biomedicine. „We've now succeeded in combining the genetics of yeast, which has a single chromosome set that allows instant gene mutation, with



"Picture of a single (haploid) chromosome set in a mouse stem cell, produced using the new technology." Foto IMBA

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stem cell biology", he says. "For decades researchers have been looking for a system in mammals which would allow scientists to reconstruct millions of gene mutations simultaneously. We have solved the puzzle and even broke a paradigm in biology – we managed to make stable mouse stem cells with a single set of chromosomes and developed novel tools to use such stem cells to rapidly check virtually all genes at the same time for a specific function."

This new technology helped Ulrich Elling in unraveling the toxic effect of ricin. He tested the poison in thousands of different mutations of mouse stem cells, and discovered that 49 different genetic mutations were present in one single protein, Gpr107. Obviously, a mutation in this protein saved the cells.

Combination with stem cell research reveals broad range of applications

The incredible potential in this discovery becomes even clearer in the light of stem cells' ability to transform into any cell in the human body. Josef Penninger is excited. „The possible uses of this discovery are endless. They range from fundamental issues, like which genes are necessary for the proper function of a heart muscle cell, to concrete applications as we have done in the case of ricin toxicity."

Penninger's team is already working on its next projects, including studies on how tumor cells acquire resistance to chemotherapy, a key issue in the development of cancer, and how nerve cells can regenerate, to offer hope in cases of paraplegia.

ENDS

Notes to news editors:

The scientific study „Forward and Reverse Genetics through Derivation of Haploid Mouse Embryonic Stem Cells" appears in Cell Stem Cell on Friday 2 December 2011.

The study was conducted by an international consortium from Austria, Canada, Germany and the USA under the leadership of IMBA. Special thanks go to William Stanford from the Sprott Centre for Stem Cell Research at the Ottawa Hospital Research Institute, Harald von Melchner and Frank Schnütgen from the University of Cologne, Joseph Ecker from San Diego, and Johannes Zuber and Alex Stark from the IMP in Vienna.

The Institute for Molecular Biotechnology (IMBA) is a research institute of the Austrian Academy of Sciences (Österreichische Akademie der Wissenschaften).

Screening: Systematic examination for defined criteria.

RNA interference: A mechanism in cells through which genes can be switched off.

Knock-out mouse: A mouse in which one or more genes have been deactivated. This genetic alteration is often apparent in the mouse's behavior or appearance. These mice are helpful as models for studying human diseases.

Download of press pictures: *http://de.imba.oeaw.ac.at/Presse-Foto*

Contact and interview requests:

Evelyn Devuyst, Communications IMBA - Institute of Molecular Biotechnology
Tel. +43 1 797 30 - 3626
evelyn.devuyst@imba.oeaw.ac.at
http://www.imba.oeaw.ac.at