Ricin only lethal in combination with sugar

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The plant toxin ricin is one of the most poisonous naturally occurring proteins, making it an extremely dangerous bioweapon. Ricin attacks have made headlines a number of times over the years, including the spectacular "umbrella murder" in London in the 1970s, or the ricin letters addressed to Barack Obama in 2014. There is no antidote.

Ricin destroys cells' ribosomes, rendering one of the fundamental processes required for life inactive. Even minute doses can kill within 36 to 72 hours. The plant that produces the lethal poison, Ricinus communis, is also found in some front gardens and parks. Castor oil extracted from the plant's seeds has medical and industrial uses.

Scientists have been searching for an effective ricin antidote for decades. However, cytotoxins like ricin also provide important insights into the molecular characteristics of cells, such as the contact points the poison uses to enter cells. There is also the question of how cells can protect themselves.

Ricin requires access code containing sugar

IMBA researchers have now discovered that sugar is a key factor. The researchers identified two genes that make ricin so lethal. Fut9 and Slc35c1 regulate metabolism of a particular sugar in cells, an essential monosaccharide called fucose – not to be confused with fructose or fruit sugar. Fucose attaches to proteins and is subsequently able to change their form and function. Because fucose also attaches to proteins in the cell wall, it plays an important role in communication and transport

between cells and their surroundings. As reported in *Cell Research*, both Fut9 and Slc35c1 are responsible for ricin's toxic effect because they give the poison access to cells' transport systems, enabling it to reach the ribosomes, which it ultimately destroys.

"Inhibiting these genes, for instance by means of a synthesised molecule, obstructs the transport of ricin into the cells and stops it from reaching the ribosomes, where it can unleash such significant damage. This is because the poison requires a typical sugar signature on the cell wall to which it can attach," said Jasmin Taubenschmid, a PhD student in the IMBA team headed by Josef Penninger.

Taubenschmid and protein researcher Johannes Stadlmann are the lead authors of the recently published study. The research also delivers new insights into the interplay between proteins and sugar, which plays a part in fundamental biological processes. "Previous research looked at proteins and sugar separately. But it turns out that the interaction between them is particularly fascinating, and this has generated an entirely new level of information," Stadlmann said.

A special partnership with the University of Münster and Heidelberg University shed light on the mechanism through which the poison has an effect. University hospital departments provided the IMBA research team with cell samples from a patient who was unable to metabolise fucose due to an extremely rare genetic defect. He was one of only a handful of people who might have survived an attempted umbrella murder. This is because ricin is not toxic without this particular sugar. "Research into rare diseases often produces astonishing findings that are useful to a large number of people," said IMBA Scientific Director Josef Penninger.

More information: Stadlmann, Taubenschmid et al., "A vital sugar code for ricin toxicity", *Cell Research* 2017. DOI: 10.1038/cr.2017

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