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Baneful beans

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Castor oil was part of our grand parents' first-aid cabinets. Already widely used in ancient medicine, it became particularly popular in the 20th century and, like Vin Mariani[1], it was the remedy to an endless list of human ails. Castor oil is derived from castor beans, which are the seeds of *Ricinus communis* – a plant native to tropical Southeast Africa grown worldwide today. Pleasing in appearance and seemingly harmless, a castor bean – like Dr Jekyll – has a nasty side to it. Besides the oily salve, the beans also produce a toxin known as ricin, which is left behind in the mash in the process of oil extraction. Ricin is lethal to men and has – like botulinum toxin[2] and anthrax – been extensively studied in the event of its use as a bioweapon. Stalin's chief of the secret police, Lavrenti Beria, was summoned to develop poisons and assassination techniques, which were still in use well after his death. One notorious invention was the ricin-loaded platinum pellet which was fired into the thigh of the Bulgarian dissident Georgi Markov by way of an umbrella in London, in 1978.

The term 'ricin' was coined by the taxonomist Carl Linnaeus (1707-1778), who noted the physical resemblance of the mottled castor bean with a blood-gorged tick, or '*ricinus*' in Latin. The term 'castor' stems from a taxonomic error… The first English traders mistook *Ricinus communis* for another bean species *Vitex agnus-castus*, hence the designation 'castor' oil in English.

Ricinus communis

Courtesy of Sandrine Pilbout, SIB Geneva

Why would a plant produce such a toxin in the first place? There is no definite answer yet besides the usual 'defence mechanism theory'. Ricin represents 5% of the bean's contents, where it is synthesized in the endosperm cells of maturing seeds and then stored in vacuoles. Once the seeds have germinated, the toxins are degraded in a matter of days. So it does not seem such a wild idea to assume that the toxins are there to avoid bean consumption, to give it a chance to germinate. Ricin is toxic to most animals and insects. However, if the bean is swallowed whole it will glide through the gastrointestinal tract and simply appear at the other end. But bitten bean can kill; the ricin-content of twenty chewed beans is enough to kill a man.

Ricin kills by attacking the 28S ribosomal RNA; protein synthesis is then blocked and the cell dies. To do this, however, ricin has to find its way into the cell's cytosol. How? Ricin is a heterodimer of two globular chains – A and B – which have specific functions. Chain A is the killer; chain B is its escort. Chain B looks like a barbell into which is squeezed the A chain. Each of the B chain's 'heavy weights' has a galactoside binding site. Once released from the bean, chain B bolts for cell-surface carbohydrates dragging the A chain along with it. Once bound to its ligand, the B chain enters the cell via endocytosis.

Trapped in an endosome, ricin then follows a remarkable route. While the normal course of protein maturation starts in the endoplasmic

reticulum (ER) and ends in the Golgi apparatus, ricin starts its journey in the Golgi apparatus and makes its way into the ER. How does it find its path? By way of endosomes? Or are there molecules which carry it from one compartment to the other? No one knows. It could be either process.

Once in the ER, there is one last hurdle: the A chain has to find its way out into the cytosol to attack its prey. The current theory is that it may use what is known as the Sec61p complex – a complex which carries unwanted proteins from the ER into the cytosol to undergo hydrolysis. The A chain could benefit from this shuttle and hitch a ride into the cytosol. Shunning hydrolysis it could then turn onto its target – the 28S ribosomal RNA – and inactivate it by snapping off an adenine residue from an exposed RNA loop. This particular loop is involved in the binding of elongation factors. Net result: protein synthesis is checked. One ricin A chain can inactivate about 2000 ribosomes per minute… Which is why the weight of a single grain of salt (ca. 70 micrograms) is enough to kill an adult and 1g of purified ricin is enough to kill 36000 people!

The killer quality of ricin could help in finding one way of fighting off cancer. The A chain coupled to an antibody whose target is a specific cell – e.g. a cancer cell – could kill the cell specifically. Such a chimeric molecule is known as a 'magic bullet' – a term coined by the famous German immunologist Paul Ehrlich (1854-1915) in the late 19th century. This form of chemotherapy is particularly valuable since the toxins would be aimed at a specific type of cell and not all cell types, thereby killing off only the cells which are ill. The problem though is finding a suitable substitute for the B chain, i.e. a substitute which would take the A chain to its correct target. A further problem is that the A chain tends to trigger a heavy immune response…

With the threat of bioterrorism hovering over our heads, a ricin vaccine would not be redundant, which is why the knowledge of the precise 3D structure of ricin is essential. To this end, in the early 1990s ricin was sent into space in the hope that the loss of gravity would produce perfect ricin crystals. Unfortunately, the crystals turned out to be of poor quality and undersized – the vibrations of the shuttle as it re-entered the earth's atmosphere were far too violent, and scientists had to resort to the X-ray diffraction patterns derived from classically-obtained crystals…

Cross-references to Swiss-Prot

Ricin, *Ricinus communis* (Castor bean) : P02879

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