Targeting toxin trafficking

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Toxins produced by plants and bacteria pose a significant threat to humans, as emphasized by the recent effects of cucumber-borne Shiga toxin in Germany. Now, new research published on July 21st by the Cell Press journal *Developmental Cell* provides a clearer view of the combination of similar and divergent strategies that different toxins use to invade a human host cell.

Ricin is a highly toxic protein derived from the castor bean plant that has raised concerns as a potentially lethal biological weapon. Pseudomonas Exotoxin A (PE) is a sometimes deadly protein produced by a common bacterium that can infect the lungs and urinary tract. "Although from very different origins, both PE and ricin share several points in common," says senior study author, Dr. Frédéric Bard from the Institute of Molecular and Cell Biology in Singapore. "Like many other toxins, they have evolved mechanisms for hijacking intracellular membrane transport processes." Previous research has identified some of the proteins made by our own cells that are used by the toxins. In theory, disrupting these proteins, or the genes that make them, could serve as a useful toxin antidote. However, the extent to which different toxins share requirements for the host proteins they use was not clear.

Dr. Bard and colleagues discovered that many different proteins are required for maximum toxicity of ricin and PE, and the requirements of both toxins differ significantly and at multiple levels. However, the pathways used by the toxins do exhibit some similarities. "Interestingly, the toxins share some genetic requirements, and exhibit similar sub-cellular localizations at various levels of their trafficking, suggesting two

intertwined pathways converging and diverging at multiple levels," explains Dr. Bard.

Although the reason for this complexity is not clear, understanding toxin trafficking at the genetic level may prove useful for designing treatments that target these and other similar potentially deadly toxins. "Our study provides a number of potential therapeutic targets to design specific toxin antidotes. Understanding and targeting specific pathways will likely allow a better control of possible side effects," concludes Dr. Bard. "Additionally, the high number of genes involved also suggests that synergistic drug therapies against these types of toxins could be designed."

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