Poster Presentation

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The structure of an ABC toxin particle determined by X-ray crystallography and single particle EM.

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The ABC toxin complexes produced by certain bacteria are of interest owing to their potent insecticidal activity and potential role in human disease. These complexes comprise at least three proteins (A, B and C), which must assemble to be fully toxic. The carboxy-terminal region of the C protein is the main cytotoxic component, and is poorly conserved between different toxin complexes. A general model of action has been proposed, in which the toxin complex binds to the cell surface via the A protein, is endocytosed, and sub-sequently forms a pH-triggered channel, allowing the translocation of C into the cytoplasm, where it can cause cytoskeletal disruption in both insect and mammalian cells. We have determined the three-dimensional structure of the complex formed between the B and C proteins by X-ray crystallography to 2.5Å. These proteins assemble to form an unprecedented, large hollow structure that encapsulates and sequesters the cytotoxic, C-terminal region of the C protein like the shell of an egg. The shell is decorated on one end by a β-propeller domain, which mediates attachment of the B–C heterodimer to the A protein in the native complex. The structure reveals how C auto-proteolyses when folded in complex with B. The C protein is the first example of a structure that contains rearrangement hotspot (RHS) repeats, and illustrates a striking structural architecture that we predict to be conserved across both this widely distributed bacterial protein family and the related eukaryotic tyrosine-aspartate (YD)-repeat-containing protein family, which includes the teneurins. The structure provides the first clues about the function of these protein repeat families, and suggests a generic mechanism for protein encapsulation and delivery. We have been able to model the complete ABC toxin complex for the by docking the B–C complex and both associated chitinase enzymes, Chi1 and Chi2, onto the single-particle electron microscopy structure of the Y. entomophaga A pentamer. The structure of the complete complex presented here reveals how the cytotoxic C proteins of ABC-type toxin complexes are processed and protected, demonstrates the function of the B protein within the complex and provides a framework for further experiments to build a complete mechanistic model of action for this class of toxins. More broadly, it also illuminates the function of the widely distributed RHS- and YD-repeat families of proteins, which had previously been unknown.

[1] *Busby, J. N., Panjikar, S., Landsberg, M. J., et al. (2013) The BC component of ABC toxins is an RHS-repeat-containing protein encapsulation device. Nature 501, 547–550.,* ***[2]*** *Busby, J. N., Landsberg, M. J., Simpson, R. M., et al. (2012) Structural Analysis of Chi1 Chitinase from Yen-Tc: The Multisubunit Insecticidal ABC Toxin Complex of Yersinia entomophaga. Journal of Molecular Biology 415, 359–371.,* ***[3]*** *Landsberg, M. J., Jones, S. A., Rothnagel, et al. (2011) 3D structure of the Yersinia entomophaga toxin complex and implications for insecticidal activity. Proc Natl Acad Sci USA 108, 20544–20549*

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