Toxin family binds to sugar receptors on human cells to cause damage

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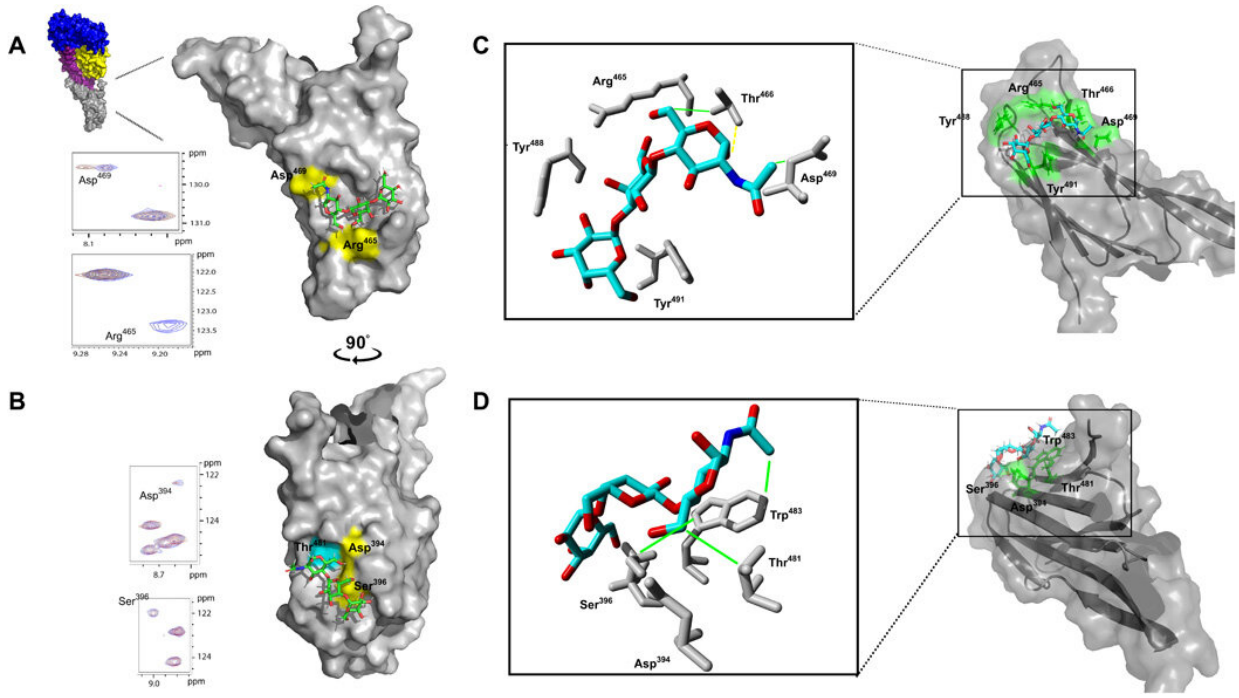

Fig. 5 NMR, molecular dynamics and site-directed mutagenesis, confirmed structures of SLY D4 engaged with two distinct glycan receptors.Sections of ^{1}H-^{15}N HSQC NMR CSP spectra of SLY D4 in the presence of αGal/Galili antigen (A) and P_1 antigen (B) at a protein:ligand ratio of 1:10. Signals of apo-SLY D4 are shown in blue and SLY D4 in complex with glycans are shown in red. Full ^{1}H-^{15}N HSQC NMR CSP spectra are shown in fig. S6 (B and C). Amino acids that showed an intensity change or CSP are highlighted in yellow in the SLY D4 structure. Unbiased docking experiments of SLY D4 with αGal/Galili antigen (C) and P_1 antigen (D) represent an energetically favored bound conformation. Both modeled structures are in excellent agreement with ^{1}H-^{15}N HSQC NMR titration experiments (see Fig. 5, A and B). Binding residues

identified in molecular docking experiments only are highlighted in cyan. Coordinating amino acids are shaded in green. Dotted yellow bars represent hydrogen bonds. Green bars represent strong hydrophobic interactions, whereas orange bars represent weaker hydrophobic interactions. For an enlarged version of (C) and (D) showing the key coordinating residues, see fig. S6D. See table S3 for SPR analysis of site-directed mutants of key coordinating residues highlighted in (A) and (B). The whole SLY toxin crystal structure is shown in blue (D1), purple (D2), yellow (D3), and gray (D4) in (A) (Protein Data Bank code 3HVN). ppm, parts per million. Credit: *Science Advances* (2020). DOI: 10.1126/sciadv.aaz4926

New Griffith University research has found that sugars decorating human cells allow toxins, produced by disease-causing bacteria, to bind to human cells and cause damage or death.

The family of toxins known as cholesterol-dependent cytolysins (CDCs), are produced by bacteria such as Streptococcus pneumoniae, group A Streptococcus and Listeria monocytogenes, which cause pneumonia, invasive group A Strep disease (including what is known as flesh-eating disease) and listeriosis.

These toxins damage human cells by forming pores in the membrane which cause the cells to break open.

In a paper published in *Science Advances* today, the Institute for Glycomics researchers leading an Australian and international team found found that cell specific sugars are the targets for eight major CDCs and not only cholesterol, as previously thought.

Lead researcher Dr. Lucy Shewell said they could stop the toxins causing damage to human blood cells by adding in the binding sugars.

"By adding sugars in solution with the toxins, the toxins are effectively mopped up before they do any damage to the red blood cells.

"The CDCs still need cholesterol in the membrane to allow them to form the final pore, but they need to bind to the sugars to recognise the cells they kill,"' Dr. Shewell said.

"Our research has shown that it is actually specific sugars on the cell surface which are the binding targets for these toxins. We have also identified the part of the toxin responsible for sugar binding.

"Understanding to which sugars these toxins bind gives us greater insight into which cells they damage and can allow us to develop therapeutics to block their harmful action."

Corresponding author of the study, Professor Michael Jennings said, "This research provides new information that will guide development of small molecule drugs and new vaccines that targets these toxins."

Professor Mark von Itzstein AO, Director of the Institute for Glycomics, said this was another excellent example of how the Institute's unique research approach centred around 'glycomics' can pave the way to new translational outcomes in their ongoing fight against some of the most debilitating diseases.

More information: Lucy K. Shewell et al. All major cholesterol-dependent cytolysins use glycans as cellular receptors, *Science Advances* (2020). DOI: 10.1126/sciadv.aaz4926

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