Professor Alexander WLODAWER

How to Turn the Sweet Tooth of Viruses into their Achilles' Heel by Utilizing Antiviral Lectins.

Macromolecular Crystallography Laboratory,
CCR, NCI, Frederick, MD 21702-1201, USA
Email: wlodawer@ncifcrf.gov

Surfaces of viral glycoproteins are covered by complex sugars that differ substantially from the carbohydrates found on the proteins of the host organisms. A number of lectins have now been isolated from cyanobacteria that are capable of sub-nanomolar binding of branched carbohydrates, principally those that contain mannose residues, thus preventing the possibility of interactions between the viruses and the cells. We have been investigating crystal structures of several such lectins, including cyanovirin, scytovirin, and griffithsin. Whereas cyanovirin exists in either monomeric or dimeric form, the other two lectins are obligatory dimers. Crystal structure of griffithsin was solved by SAD and refined at 1.3 Å resolution for the free lectin and at 0.94 Å as a complex with mannose. Griffithsin molecules form a domain-swapped dimer, in which two β-strands of one molecule complete a β-prism consisting of three four-stranded sheets, with an approximate three-fold axis, of another molecule (and vice versa). The structure of each monomer bears close resemblance to other mannose- and galactose-specific lectins such as jacalin or heltuba, but its dimeric structure is unique. Some of the carbohydrate-binding sites of griffithsin are not present in other lectins. Griffithsin has been reported to display picomolar activity against HIV-1, inhibition over 1000-fold better than previously reported for jacalin and other monosaccharide-specific lectins. The presence of multiple binding sites may explain the high-specificity binding of mannose-containing oligosaccharides to griffithsin, the basis of its remarkable activity against viruses that cause diseases such as AIDS and SARS. Antiviral lectins are under development as components of female-controlled contraceptives that should provide a novel weapon for prevention of viral transmission.