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Antiviral lectins as potential HIV microbicides

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A growing class of potential antivirals encompasses carbohydrate-binding proteins, such as antibodies and lectins. They block virus entry into host target cells and halt virus transmission from virus-infected cells to non-infected cells, thereby preventing infection. Here, we review the structural basis for the anti-HIV activity of various lectins, describing their structures and determinants of high-affinity oligosaccharide binding. The mechanism of glycan recognition on the gp120 envelope protein by these antiviral lectins may therefore be exploited for developing agents and alternative strategies to prevent HIV transmission.

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Introduction

Despite continued and extensive research efforts over the last 30 years, there is still no cure for HIV/AIDS. Therefore, new and different strategies for preventing sexual transmission of HIV are being explored. The development of lectins as microbicidal agents for topical or *ex vivo* use represents such an alternative approach in the fight against AIDS [1–4]. Topical agents may be particularly useful for curbing the escalating rate of HIV infection in women, notably in those regions of the world where social and psychological barriers to other methods of prevention, diagnosis and treatment of HIV infections may not easily be overcome. The use of microbicides, when applied topically to genital mucosal surfaces, is potentially a powerful strategy to significantly reduce transmission of sexually transmitted viral pathogens to females, given that it is discreet and can be completely controlled by women.

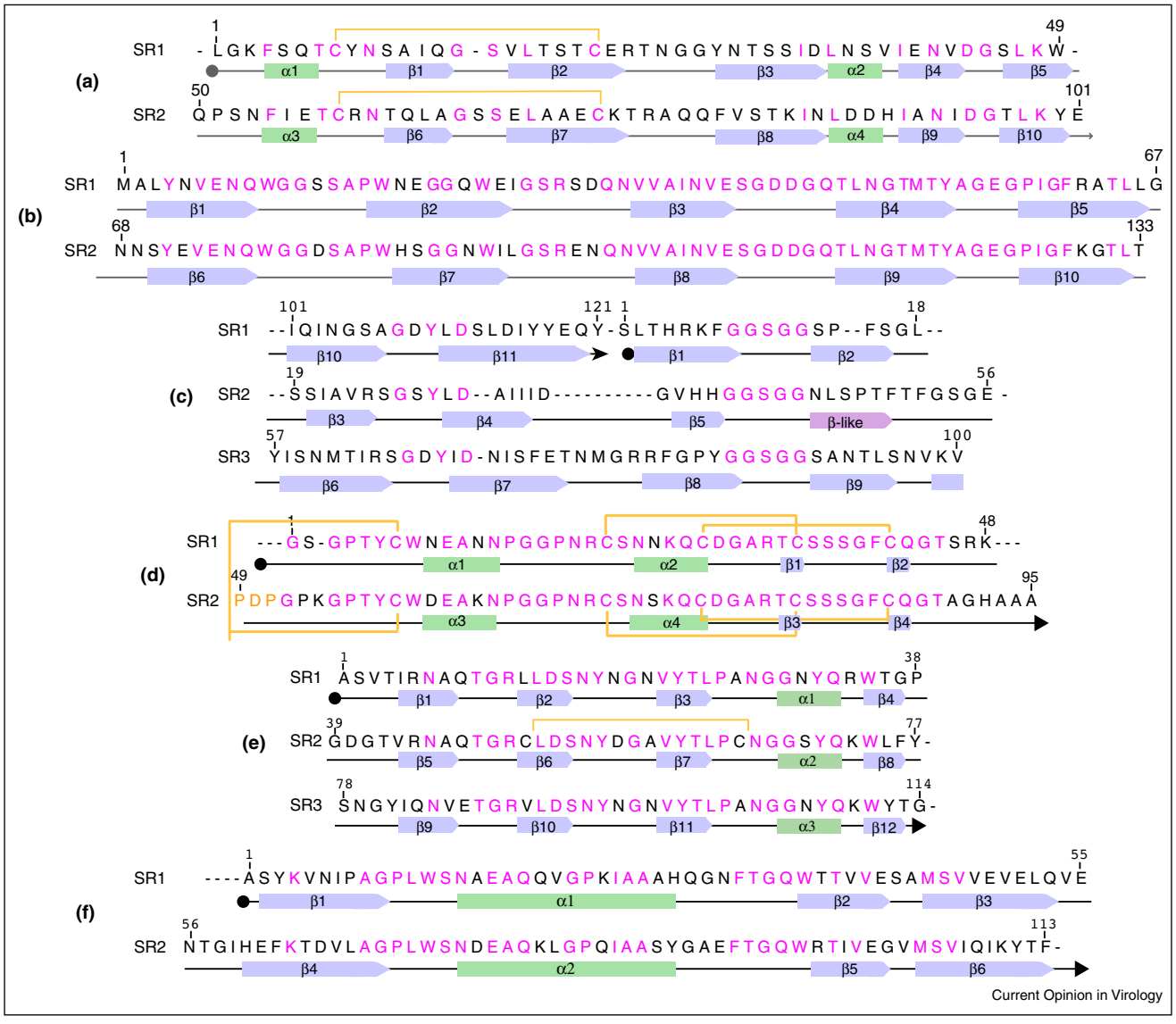
Antiviral lectins prevent infection by binding to the sugars that decorate the surface of the HIV envelope (Env) glycoprotein gp120, keeping the trimeric Env in a closed, non-fusogenic state [1,4–6]. This renders the virus unable to enter the host target cell. It also blocks direct cell-to-cell transmission between virus-infected and non-infected cells [7]. Lectins can also efficiently abrogate DC SIGN-mediated HIV-1 capture and subsequent transfer to T lymphocytes [8]. In order to illustrate the molecular basis of their HIV-inactivating properties, we review the atomic structures, the distinct modes of glycan recognition and oligosaccharide binding epitopes of Cyanovirin-N (CV-N), *Oscillatoria agardhii* agglutinin (OAA), Griffithsin (GRFT), Scytovirin (SVN), *Microcystis viridis* lectin (MVL), and Actinohivin (AH).

Antiviral lectins: similarities and differences

CV-N, OAA, GRFT, SVN, MVL, and AH exhibit potent anti-HIV activity, with IC_{50} values in the nanomolar–picomolar range. They were discovered and isolated from a variety of cyanobacterial or algal species. For example, CV-N was found in an aqueous extract from the cyanobacterium *Nostoc ellipsosporum* [7,9], OAA in the *O. agardhii* strain NIES-204 [10,11], SVN in *Scytonema varium* [12], and MVL was isolated from the freshwater bloom-forming cyanobacterium *M. viridis* NIES-102 [13]. In addition, GRFT was isolated from the red alga *Griffithsia* sp. [14], collected from the waters off New Zealand, and AH from the actinomycete *Longisporum Albid* (actinomycete strain K97-0003) [15,16]. Most importantly, the atomic structures of these lectins have helped to elucidate the basis of their antiviral activity, and their interactions with the relevant high mannose glycans of gp120, revealed either by X-ray crystallography or NMR spectroscopy, yield important details on their distinct modes of glycan recognition, both on the protein and oligosaccharide epitopes.

All the above lectins exhibit different tertiary and quaternary structures. Interestingly, however, they all contain internal repeats within the primary sequences (Figure 1). CV-N, OAA, SVN, and MVL possess two sequence repeats. In CV-N, the two tandem repeats comprise residues 1–50 (sequence repeat 1; SR1) and residues 51–101 (sequence repeat 2; SR2) [9]. Each repeat possesses a disulfide bond, C8–C22 in SR1 and C58–C73 in SR2 (Figure 1A) [9,17,18]. In OAA, residues 1–67 and residues 68–133 make up sequence repeat 1 (SR1) and sequence repeat 2 (SR2), respectively. The OAA repeats exhibit ~80% sequence identity between SR1 and SR2 (Figure 1B) [11,19]. The SVN sequence also contains sequence duplication for residues 1–48 and residues 49–95 (Figure 1D) [12]. Interestingly, SVN possesses a large number of cysteine residues, ten in total [12] forming five disulfide bond between C7–C55, C20–C32, C26–C38,

Figure 1



Sequence alignment of CV-N **(A)**, OAA **(B)**, GRFT **(C)**, SVN **(D)**, AH **(E)** and MVL **(F)** illustrating the sequence repeats. Conserved residues between repeats are highlighted in magenta. Disulfide bonds, alpha helices and beta strands are indicated and colored in yellow, light green and light purple, respectively.

C68–C80, and C74–C86 (Figure 1D) [20,21]. The two sequence repeats in MVL each contain 54 amino acids that are ~50% identical (Figure 1F) [13].

GRFT and AH contain three sequence repeats. In GRFT, SR1 comprises residues 1–18 and residues 101–121, SR2 spans residues 19–56, and SR3 contains residues 57–100 (Figure 1C). In addition, distinct sequence motifs were noted in two loop regions, namely GxYxD and GGSGG motifs (Figure 1C). AH's three repeats SR1, SR2, and SR3 encompass residues 1–38, 39–77, and 78–114, respectively (Figure 1E) [16].

Interestingly, the number of sequence repeats often corresponds to the number of domains and binding sites in each lectin, with the exception of GRFT, where the three repeats result in three binding sites, but not three individual domains. However, the polypeptide chain of each sequence repeat does not always make up a domain; frequently individual domains of these lectins involve strand exchange between domains. The high degree of amino acid sequence similarity, ranging from ~30% in CV-N to ~81% in OAA, goes hand-in-hand with structural similarity between the individual domains.