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Fungal lectins: structure, function and potential applications

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Lectins are a widespread class of proteins implicated in many essential cellular and molecular recognition processes. They recognize carbohydrates in a non-catalytic, specific and reversible manner. Fungi, which include mushrooms, microfungi and yeasts, have attracted wide interest in recent years. They are indeed a promising source for novel lectins with unique specificity and potential for biomedical and biotechnological applications. Information on fungal lectins, particularly structural insight, is scarce compared to that on their plant and animal counterparts. This review therefore focuses on the structure, function, and exploitable properties of fungal lectins.

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Introduction

Lectins are versatile and ubiquitous proteins of non-immune origin that bind reversibly and specifically to carbohydrates. They are often multivalent which give them the well-known ability to agglutinate cells. They mediate recognition events in many biological and pathological processes: cellular signaling, differentiation, host–pathogen interactions and tissue metastasis. Lectins are highly sought proteins since they present great therapeutical and biotechnological potentials. Fungi have become a rich source for new lectins with unique carbohydrate specificities. Numerous fungal lectins have indeed been reported with 82% arising from mushrooms, 15% from microfungi (molds) and 3% from yeasts [1]. Various physiological roles have been proposed for fungal lectins even if they remain elusive in many instances (Figure 1) [2–4]. They serve as storage proteins like in plants and intervene during fungal growth, development and morphogenesis. They mediate host recognition necessary to ectomycorrhizal symbiosis [5] and association with algae or cyanobacteria in lichens [6], or yeast flocculation [7]. Fungal lectins also take part in the defense of fungi since some present toxic activities such as insecticidal, vermicidal or antiviral, and their interaction with host glycoconjugates can be involved in the infection process of pathogenic fungi as described below.

The localization, biochemical properties and biological activities of many fungal lectins have been determined [2–4]. In contrast, very few fungal lectins have been structurally characterized or produced in a recombinant form mainly because their primary sequence is generally unknown. Structural data started to become available only ten years ago and were reviewed once in 2007 [8]. Herein, we attempt to give an overview of recent structural and functional aspects of fungal lectins and on their possible applications.

Fold and quaternary association in fungal lectins

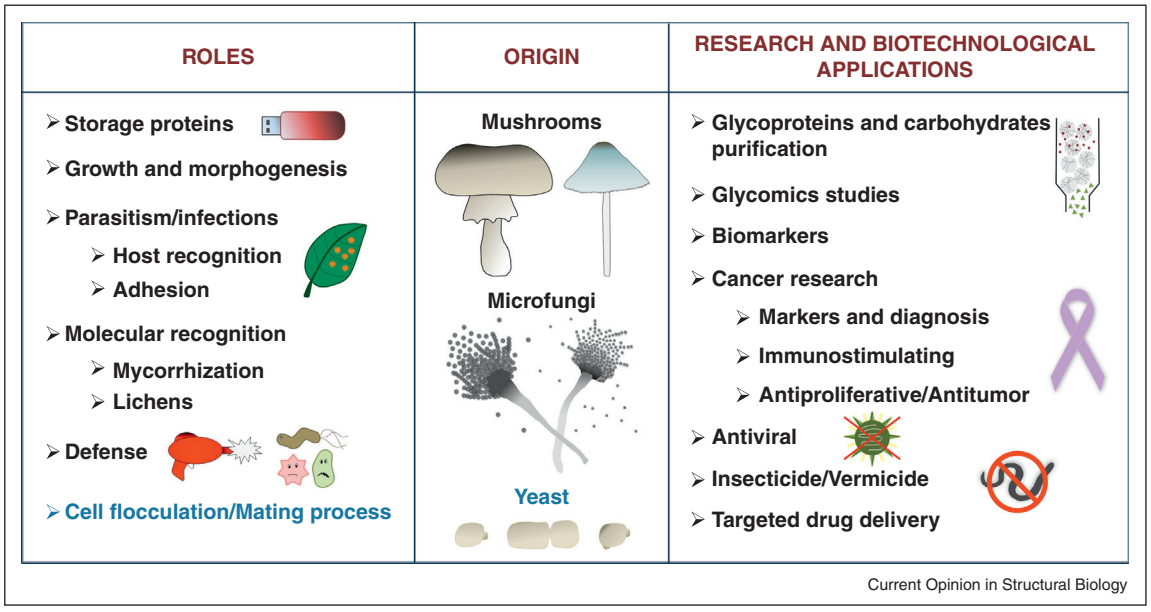
Today only 26 different fungal lectins have been structurally characterized resulting in approximately 100 crystal structures, 40% of them being in complex with carbohydrate ligands. This represents 8.5% of all lectin structures as gathered in the Lectin 3D database (http://lectin3d.cermav.cnrs.fr). Ten different folds have been identified, some of them being classical lectin or carbohydrate binding modules (CBM) folds, widely spread in all living kingdom, such as β-trefoil, β-sandwich (galectin, Ig and L-lectin types) or LysM domain.

Cyanovirin-type fold is shared with cyanobacteria while 6-blade β-propeller is observed in soil bacteria, illustrating the probable exchange of genetic material between fungi and soil inhabitants. The calcium-containing β-sandwich of flocculin has only been observed in yeasts. The integrin-like 7-blade β-propeller is unique to lectins from fungi, as well as the actinoporin-like fold, also called fungal fruit body lectin fold. Representatives of the major classes are described below.

Galectins constitute a conserved family of β-galactoside-binding proteins present in vertebrates, invertebrates and in some fungi [9]. Galectins from *Agrocybe aegerita* AAL [10] and *Coprinopsis cinerea* CGL2 [11] present the prototype galectin fold which consists of a β-sandwich formed by two parallel 6 stranded antiparallel β-sheets, one of them forming a concave surface specialized in the binding of β-galactosides (Figure 2a). While prototype lectins are usually dimeric, the *C. cinerea* galectins have the particularity to be tetrameric assembling as four-leafed clover [12].

Lectins from the fruiting bodies of several fungi such as *Boletus edulis* BEL [13], *Xerocomus chrysenteron* XCL [14],

Figure 1



Roles and potential applications of fungal lectins.

Agaricus bisporus ABL [15] and *Sclerotium rolfsii* SRL [16] present an actinoporin-like fold which consists of a β-sandwich made by two β-sheets composed of six and four β-strands respectively and connected by a helix-loop-helix motif (Figure 2b). Those lectins form dimers or tetramers with two distinct binding sites on each monomer found on each side of the helix-loop-helix motif. The primary site is specific for GalNAc while the secondary site is specific for GlcNAc.

The β-trefoil fold, or ricin-B fold, is very versatile and characterized by three subdomains α, β, and γ assembled around a pseudo-3-fold axis. A four-stranded β-sheet composes each subdomain that can present one carbohydrate-binding site (Figure 2c). The lectins from *Polyporus squamosus* PSL [17] and *Marasmius oreades* MOA [18] present an additional domain at the C-terminus involved in dimerization. The pore forming lectin from *Laetiporus sulphureus* LSL is hexameric and presents an elongated C-terminal domain belonging to the aerolysin family of β-pore-forming toxins [19]. The *Sclerotinia sclerotiorum* agglutinin SSA [20] and *Coprinopsis cinerea* lectin CCL2 [21••] are monomeric while the *Boletus edulis* lectin BEL β-trefoil [22], the *Clitocybe nebularis* lectin CNL [23] and the *Rhizoctonia solani* agglutinin RSA [24] present various dimeric associations. Presence and orientation of key residues define the functionality of the three potential carbohydrate binding sites. In the case of MOA and BEL β-trefoil, all binding sites are functional while only the site of subdomain α or γ is functional for CNL or SSA respectively.

Several fungal lectins are homologs of the cyanovirin-N (CVNH), a small viricidal lectin produced by the cyanobacterium *Nostoc ellipsosporum*. They are monomeric and mostly belong to type I CVNH with one copy of cyanovirin-N such as GzCVNH lectin from the wheat head blight fungus *Gibberella zeae* [25]. GzCVNH consists of two CVNH repeats related through a pseudo twofold symmetry referred to as domain A and B. Carbohydrate binding can occur in both domains but often only one binding site is functional in the fungal CVNHs. The structure of MOCNVH-LysM from *Magnaporthe oryzae* gave the first structural insights for type III CNVH where a LysM domain is inserted between the two CNVH repeats (Figure 2d) [26••]. The LysM domain recognizes chitin oligomers while the CNVH part binds oligomannosides in both A and B domains.

Yeast adhesins involve in flocculation like Flo5 from *Saccharomyces cerevisiae* [7] or in epithelial adhesion like Epa1p from the human pathogen *Candida glabrata* [27•,28••] present at their N-terminus a lectin domain with a β-sandwich topology that resembles the PA14 domain from the anthrax toxin protective antigen. A calcium-dependent carbohydrate-binding site is found opposite to the N and C-termini that are tethered by disulfide bridges (Figure 2e). The calcium ion is bound through a D*cis*D motif in a surface loop. Flo5 presents also a secondary binding site and a Flo5 subdomain, stabilized by two disulfide bridges and composed of five short β-strands that helps to discriminate oligomannosides. [7].

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