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Lectins in human pathogenic fungi



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ABSTRACT

Lectins are carbohydrate-binding proteins widely distributed in nature. They constitute a highly diverse group of proteins consisting of many different protein families that are, in general, structurally unrelated. In the last few years, mushroom and other fungal lectins have attracted wide attention due to their anti-tumour, antiproliferative and immunomodulatory activities. The present mini-review provides concise information about recent developments in understanding lectins from human pathogenic fungi. A bibliographic search was performed in the Science Direct and PubMed databases, using the following keywords “lectin”, “fungi”, “human” and “pathogenic”. Lectins present in fungi have been classified; however, the role played by lectins derived from human pathogenic fungi in infectious processes remains uncertain; thus, this is a scientific field requiring more research.

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Lectinas en hongos patógenos para el ser humano

RESUMEN

Las lectinas son proteínas que se unen a los hidratos de carbono y están ampliamente distribuidas en la naturaleza. Constituyen un grupo muy diverso de proteínas incluidas en muchas familias que en general carecen de relación estructural. En los últimos años, se ha prestado mucha atención a las lectinas fúngicas debido a sus actividades antitumorales, antiproliferativas e inmunomoduladoras. La presente revisión proporciona información sucinta sobre los progresos recientes acontecidos en la comprensión de estas moléculas a partir de hongos patógenos para el ser humano. Emprendimos una búsqueda bibliográfica de los estudios publicados en las bases de datos Science Direct y PubMed, usando las palabras claves: «lectin» (lectina), «fungi» (hongos), «human» (humano) y «pathogenic» (patogénico). Se han clasificado las lectinas presentes en los hongos; sin embargo, el papel que desempeñan en los procesos infecciosos de hongos patógenos para el ser humano sigue por dilucidar, por lo que este es un ámbito científico que requiere mayor investigación.

Este manuscrito forma parte de la serie de artículos presentados en el «V International Workshop: Molecular genetic approaches to the study of human pathogenic fungi» (Oaxaca, México, 2012).

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More than 70,000 species of fungi have been described, and it is likely that many more exist. The known species include yeasts, moulds, rusts, smuts, puffballs, and mushrooms. The study of these eukaryotes has been motivated by their unique and fascinating biology, their many useful products (including wine, cheese, and antibiotics), their utility as experimental systems for basic

biology and protein expression, and their relevance as animal and plant pathogens. Fungi are eukaryotic heterotrophs and absorb food from their environment. They are non-motile and have life cycles that incorporate both sexual and asexual reproduction. They typically have elongated filaments or hyphae, which have cell walls that comprise complex polysaccharides including mannans, galactans, glucans, and chitin. There are four major phyla of fungi; each of them is extremely diverse, and fungi are assigned to a phylum on the basis of their mechanism for producing asexual spores. These phyla are the Chytridiomycota (primitive aquatic fungi),

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Mucoromycotina (e.g., black bread mould, *Rhizopus nigricans*), Ascomycota (e.g., *Saccharomyces*, *Candida*, *Aspergillus*, *Neurospora*, and more mushrooms), and Basidiomycota (e.g., mushrooms, rot fungi, and puffballs). Some fungi are extremely beneficial to humans (e.g., the yeast *Saccharomyces*, which is used in fermentation) and some are not (e.g., pathogenic yeasts such as species of *Candida* and *Cryptococcus*).⁶

Lectins are a well-known class of multivalent carbohydrate binding proteins of non-immune origin that recognize diverse sugar structures with a high degree of specificity.²⁴ Lectins have been involved in cellular signalling, malignancy, host pathogen interactions, scavenging of glycoproteins from the circulatory system, cell–cell interactions in the immune system, differentiation and protein targeting to cellular compartments.²³ Plant and animal lectins are subjected to extensive studies^{6,19} and very little information is available on lectins from fungi. However, the first fungal lectin, called «lectin phallin», was reported in 1891 by Kobert from *Amanita phalloides*,¹² which was later identified as a haemolytic agent.³⁰ In the last few years, mushroom and other fungal lectins have attracted wide attention due to their antitumour, antiproliferative and immunomodulatory activities.⁴ More recently, several reports on lectins from lower and pathogenic fungi have shown their physiological role still remains uncertain.³⁰

Fungal lectins

Fungal lectins have been isolated from mycelium,¹⁴ sporomes,¹⁰ conidia,²⁹ basidiomes,⁹ and fruiting bodies.²⁸ Fungal lectins have been classified according to their structure in the following families:

- 1. Family resembling β -propeller-fold lectins.** β -propellers are toroidal folds in which repeated four-stranded β meanders are arranged in a circular and slightly tilted fashion, like the blades of a propeller, *Aleuria aurantia* has this folding type, with six blades. This lectin is a dimer of two identical subunits of about 36 kDa, each of them binding preferably α 1,2 linked fucose residues. *A. aurantia* lectin binds preferentially to fucose linked (α 1,6) to N-acetylglucosamine, or to fucose linked (α 1,3) to N-acetylglucosamine related structures.⁸
- 2. Family resembling actinoporin-like lectin.** Actinoporins are potent eukaryotic pore-forming toxins specific in sphingomyelin-containing membranes. They are structurally similar to members of the fungal fruit-body lectin family that bind cell-surface exposed Thomsen–Friedenreich antigen (Tf antigen). *Agaricus bisporus* lectin is a tetramer and each monomer presents a novel fold with two beta sheets connected by a helix-loop-helix motif. The T-antigen disaccharide, Gal β 1,3GalNAc, a mediator of the antiproliferative effects of the protein, binds at a shallow depression on the surface of the molecule. The binding of N-acetylgalactosamine overlaps with that moiety of the T antigen but, surprisingly, N-acetylglucosamine, which differs from N-acetylgalactosamine only in the configuration of epimeric hydroxyl 4, binds at a totally different site on the opposite side of the helix-loop-helix motif. Thus, this lectin has two distinct binding sites per monomer that recognize the different configuration of a single epimeric hydroxyl.⁵
- 3. Family resembling β -trefoil domain lectin.** This type of lectin has a barbell-like structure lacking alpha-helices or beta-sheets where individual lobes contain subdomains able to bind oligosaccharide. Lectins from *Clitocybe nebularis*, *Coprino psiscinerea*, *Laetiporus sulphureus*, *Marasmius oreades*, *Polyporus squamosus*, and *Sclerotinia sclerotiorum* belong to this family. The recombinant lectin of *C. nebularis* (rCNL) agglutinates human

Table 1
Fungal lectins.

| Source | Molecular mass (kDa) | Specificity |
|--------------------------------|----------------------|---|
| <i>Agaricus blazei</i> | 70 | Glycoproteins ¹³ |
| <i>Amanita pantherina</i> | 43 | Mucin ³¹ |
| <i>Clitocybe nebularis</i> | 33 | Asialo-fetuin and lactose ²¹ |
| <i>Lactarius deliciosus</i> | 37 | Gal β 1-3GalNAc ⁹ |
| <i>Macrophomina phaseolina</i> | 34 | N-Acetylneuroaminic ³ |
| <i>Aspergillus oryzae</i> | 35 | Fucose ¹⁸ |

blood group A erythrocytes and is specific for the unique glycan N,N'-diacetylglucosamine (GalNAc β 1,4GlcNAc, LacdiNAc), as demonstrated by glycan microarray analysis (Table 1). The crystal structures of rCNL together with lactose and LacdiNAc, define its interactions with the sugars. CNL is a homodimeric lectin, each of whose monomers consists of a single ricin B lectin domain with its β -trefoil fold and one carbohydrate-binding site.²²

- 4. Family resembling galectin.** The galectin family of naturally occurring galactoside-binding lectins are expressed intracellularly and extracellularly by many cell types.¹⁶ Galectins regulate many critical cell processes, including differentiation, maturation, activation, migration, and apoptosis.¹¹ Lectins from *Agroclype cylindracea* and *C. psiscinerea*, have been isolated. Galectin from the edible fungus *A. cylindracea* (ACG) has a strong preference for N-acetylneuraminyl lactose (NeuAc α 2,3-lactose). The structure shows that ACG is a “proto”-type galectin composed of a β sandwich of two antiparallel sheets, each with six strands, in contrast to the five and six strands in animal galectins.²
- 5. Fungal immunomodulatory protein family.** *Flammulina velutipes* (Fve) lectin is a member of this family.²⁰ The lectin of this mushroom possesses immunomodulatory activity, stimulates lymphocyte mitogenesis, suppresses systemic anaphylaxis reactions and oedema, enhances transcription of IL-2, IFN- γ and tumour necrosis factor- α (TNF- α), and agglutinates red blood cells. It appears to be a lectin with specificity for cell-surface carbohydrates complex. Fve is a non-covalently linked homodimer containing Cys, His or Met residues. It shares sequence similarity only with other fungal immunomodulatory proteins (FIPs), all of unknown structure. Fve structure suggests that dimerization, critical for the activity of FIPs, occurs by 3-D domain swapping of the N-terminal helices and is stabilized predominantly by hydrophobic interactions. The structure of Fve was the first reported in this lectin family and the first of an FNIII domain-containing protein of fungal origin.²⁰

Lectins from human pathogenic fungi

Genus *Aspergillus*

Aspergillus fumigatus is responsible for severe infections in immunodeficient patients, causing invasive aspergillosis. The lectin present in *A. fumigatus* surface is of great importance for successful fixation of conidia on human epithelia. The lectin has a molecular weight of 32 kDa and is specific for terminal sialic acid residues of the carbohydrate chains.²⁹

Aspergillus oryzae is an important fermentation starter organism in the manufacture of soybean products, such as sauce and paste. However, allergic bronchopulmonary aspergillosis caused by *A. oryzae* has been reported in persons living near fermentation factories. *A. oryzae* lectin has a strong preference for the α 1,6-fucosylated sugar chain among α 1,2-, α 1,3-, α 1,4-, and α 1,6-fucosylated sugar chains.¹⁸ α -L fucopyranosyl residues are widely distributed in cell surface sugar chains and often play important

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