




Fungal infections in humans

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Master 2: Microbiology and Biological engineering

Teaching Unit "Medico-Pharmaceutical Applications of microbial biodiversity"





ImmunoPhysiology and Pharmacology

IMMUNOBIOLOGY GROUP

3s





Outline

- o Introductory aspects/epidemiology
- o Host-pathogen interactions
- o Immunity to fungal infections/immune evasion mechanisms
- o Prevention/therapy

Fungi

Somewhere between 2-11 m species:
~150 000 described

20 000 plant pathogens	600 associated with humans 150-400 human pathogens
	

Fungi are largely present in the air, dust, microbiota

Relationship with humans

Ecologic role

Probiotics

Food

Enzymes used in biotechnology

Antibiotics



Immunomodulators

Food contamination/deterioration

Toxins

Allergies

Infections



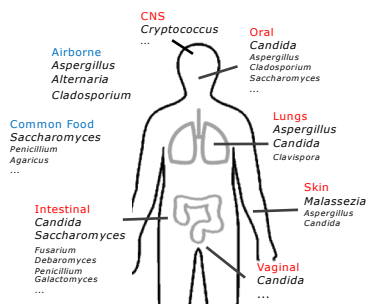
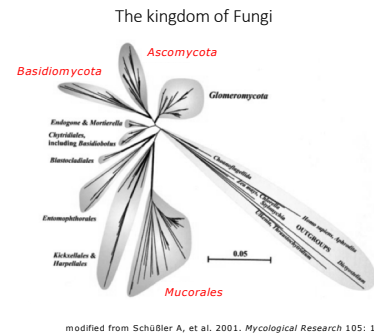
"the full impact of fungal diseases in humans is not clear"

doi: 10.1128/AAMCol.18Oct.2017

humans are usually resistant to fungal infections.

nevertheless...

human fungal infections – **mycoses** - may occur, caused by primary or opportunistic pathogens



Superficial infections of the skin and nails
25% of the world population (~1.7 billion people)
ex: athlete's foot



Mucosal infections (oral, genital)
ex: vulvovaginal candidiasis 50-70% women
in their childbearing years



Nigam & Saleh. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Akpan & Morgan. Postgrad Med J. 2002

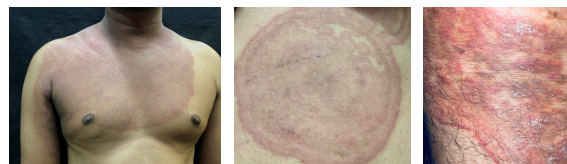
The dermatophytes

Common fungi associated with humans (20% world population infected)



The dermatophyte Genera and diseases			
Genus	Disease	Target	Transmission
<i>Trichophyton</i>	Ringworm of the scalp, body, beard, nails Athlete's foot	Hair, skin, nails	Human to human, animal to human
<i>Microsporum</i>	Ringworm of scalp Ringworm of skin	Scalp hair Skin; not nails	Animal to human, soil to human, human to human
<i>Epidermophyton</i>	Ringworm of the groin and nails	Skin; nails; not hair	Strictly human to human

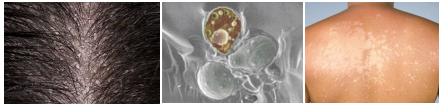
Corticosteroids can worsen ringworm
(rashes covering large body areas)



<https://www.cdc.gov/fungal/diseases/ringworm/steroids.html>

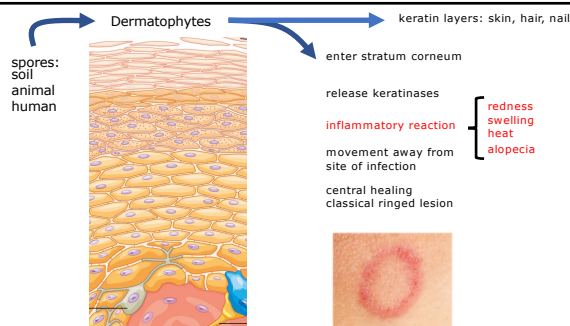
The basidiomycete *Malassezia* causes dandruff and tinea versicolor

Malassezia furfur
Malassezia globosa

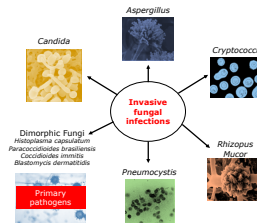


<https://www.mayoclinic.org/diseases-conditions/tinea-versicolor/symptoms-causes/syc-20378385>

Nail infections or **onychomycosis**: nail may separate from its bed, thicken, develop white spots, or become dystrophic

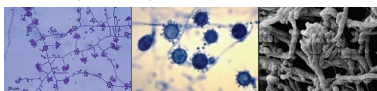


Invasive fungal infections are systemic life-threatening infections that are estimated to cause 1.5 million deaths annually



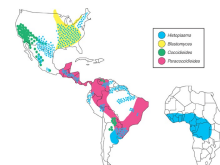
Dimorphic pathogenic fungi
Primary pathogens

- *Histoplasma capsulatum*
- *Blastomyces dermatitidis*
- *Coccidioides immitis* and *posadasii*
- *Sporothrix schenckii*
- *Talaromyces marneffei*
- *Paracoccidioides brasiliensis* (*Lacazia lobii*)

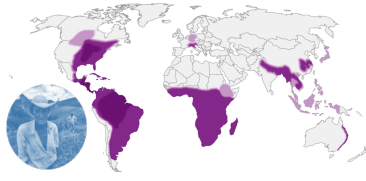



- Geographically restricted
- Acquired by inhalation
- Infect immunocompetent hosts
- Previous infection may confer immunity

- Filamentous in the environment, yeast form inside the host



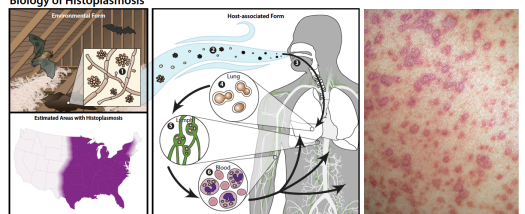
Histoplasma capsulatum

Ashraf et al. *Mycopathologia* (2020)

BEWARE OF CHICKEN DROPPINGS

Biology of Histoplasmosis



Histoplasma capsulatum

3 infectious forms:

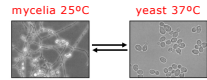
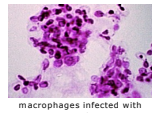
- Conidia (spores)
- Yeast
- Micellium

Risk factors:

Compromised immune system

- HIV / AIDS
- Organ transplants
- corticosteroids or TNF inhibitors
- babies ; adults > 55 years

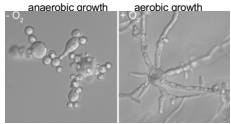
temperature
mycelia 25°C ↔ yeast 37°C

macrophages infected with *H. capsulatum*

Common opportunistic fungi and predisposing conditions	
Pathogen	Associated condition
<i>Candida</i>	Antibiotic therapy; catheters; diabetes; autoimmune diseases; corticosteroids; immunosuppression
<i>Aspergillus</i>	Leukemia; corticosteroids; immunosuppression; i.v. drug abuse
<i>Cryptococcus</i>	Diabetes; tuberculosis; cancer; corticosteroids; immunosuppression (AIDS)
<i>Pneumocystis</i>	Cancer; bone marrow or solid organ transplants; autoimmune diseases ; immunosuppression (AIDS)
<i>Zygomycota</i>	Iron overload; hematologic malignancies; organ transplantation; cancer; diabetes; corticosteroids; i.v. therapy; third degree burns

zygomycetes dimorphic growth

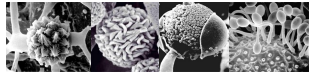


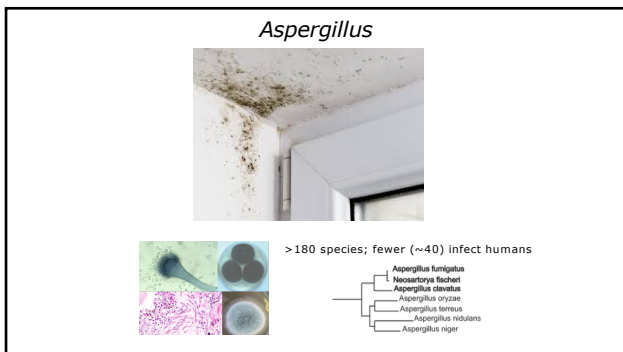
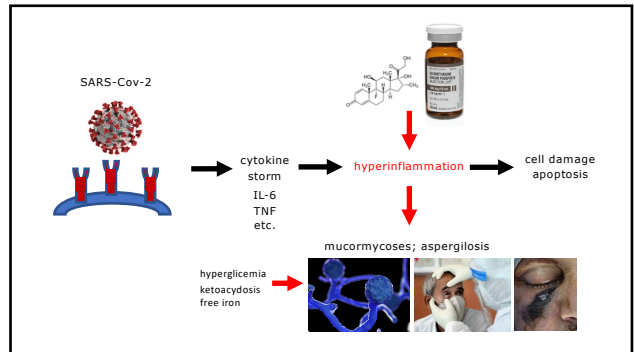
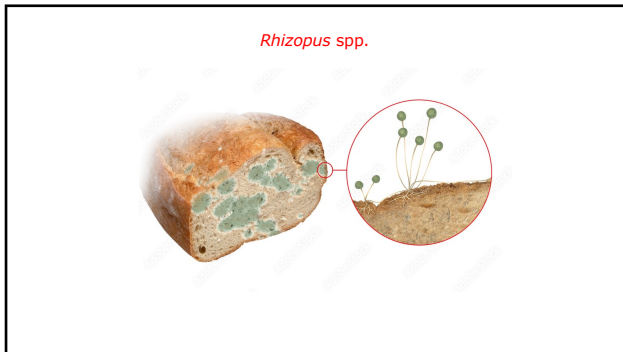
- filamentous growth in Lab culture conditions
- growth as yeast under anaerobic conditions and high CO₂

Mucormycoses *Rhizopus species* and *Mucor species*

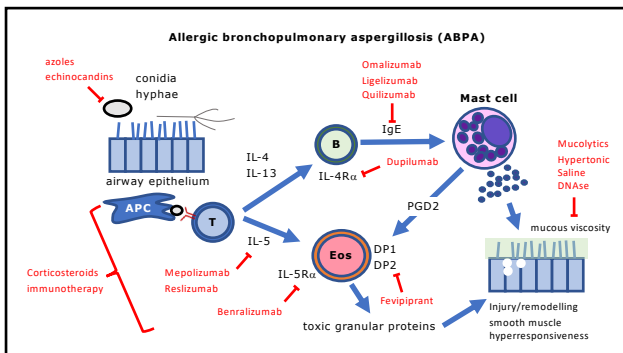
1.7 cases/million annually (Rees et al. 1998. *Clin. Infect. Dis.*)
 France: 0.7 to 1.7/million from 1997 to 2006
 Third most common fungal infection in transplanted patients

50-90% mortality
 diabetes, corticosteroids, other treatments; immunosuppressors;
 high serum iron levels





- Allergic bronchopulmonary aspergillosis (ABPA)
- Allergic *Aspergillus* sinusitis
- Aspergilloma (fungus ball)
- Chronic pulmonary aspergillosis (CPA)
- Invasive aspergillosis → cutaneous (skin) aspergillosis
- Azole-Resistant *Aspergillus fumigatus*

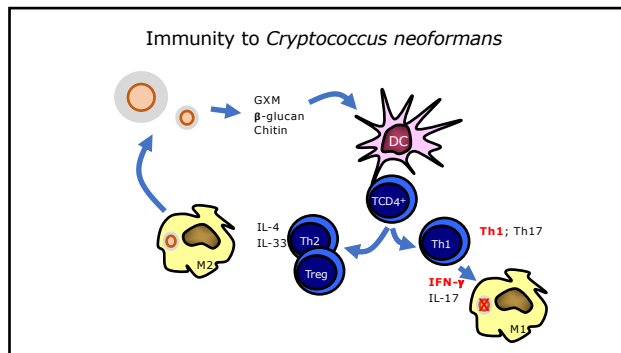
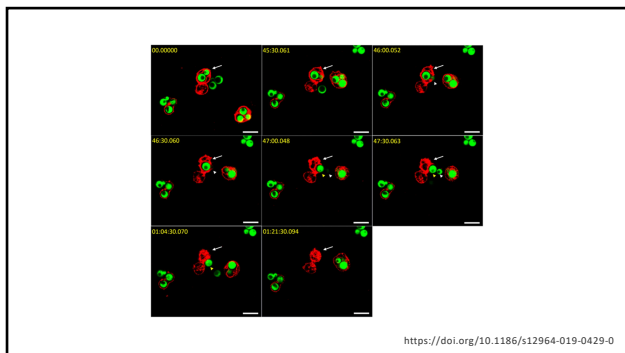
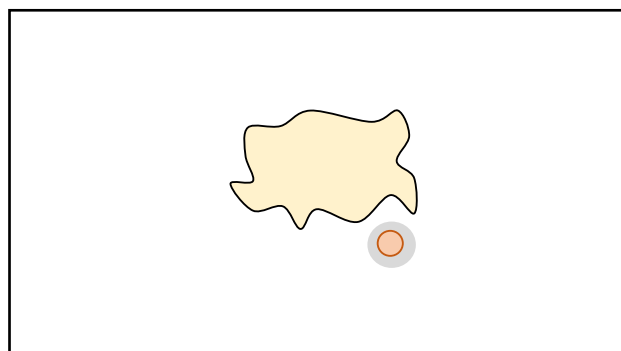
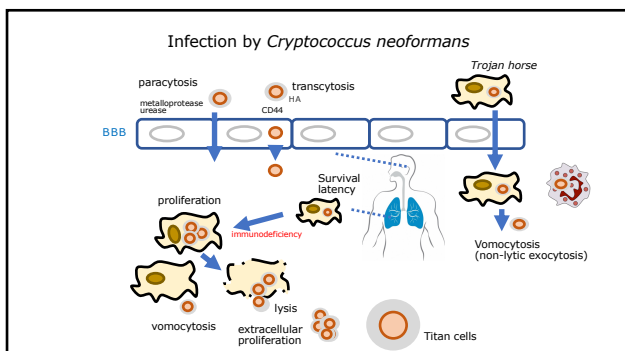
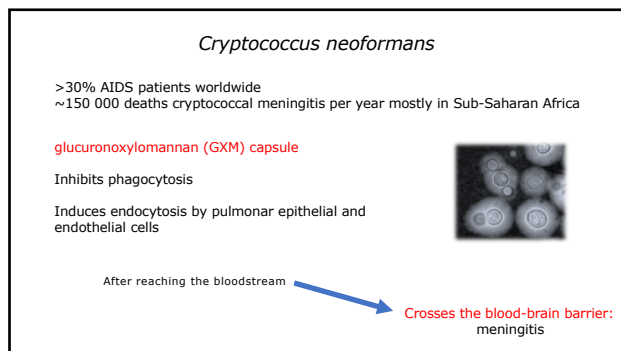
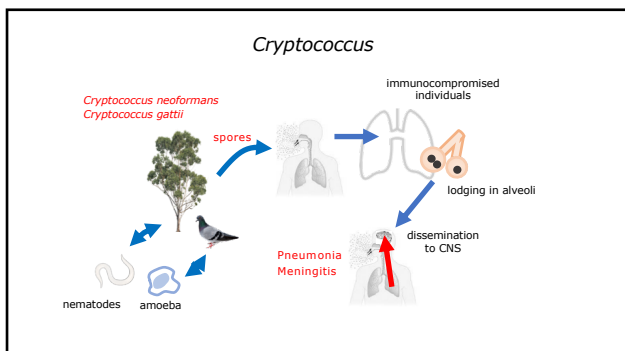


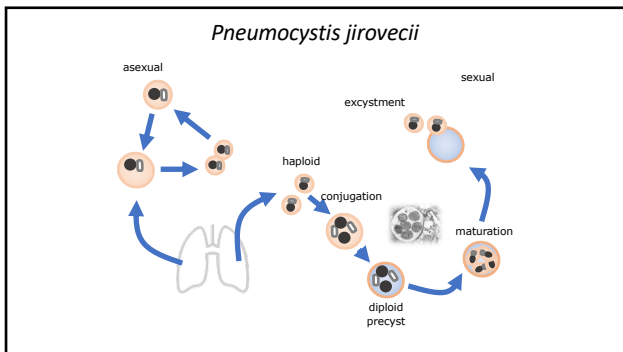
Chronic pulmonary aspergillosis: affects ~ 3 000 000 people, 240 000 Europe
 Mortality rates up to 15% (lung haemorrhage)
 Risk factor: asthma

Global burden of CPA: following pulmonary TB (prevalence of 1.74 million) complicating allergic bronchopulmonary aspergillosis (prevalence of 411 000) sarcoidosis (prevalence of 72 000)

Invasive aspergillosis: ~ 200 000/ annually
 Mortality rates up to 90%; therapy response < 30%
 13-18% incidence in bone marrow transplants and solid tumors

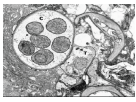
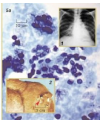
Risk factors: neutropenia; cytotoxic drugs; leukemia; steroid therapy





Pneumocystis jirovecii

- *obligatory pathogens* (non cultivable)
- direct transmission (human to human)
- infects preferentially the lungs – fast fatal pneumonia if not treated (100% fatal if untreated; 5 - 40% with treatment)
- AIDS, transplants, glucocorticoids; cancer chemotherapy






Candida

Comensals of the GI and GU tract, skin
Infection usually of endogenous origin

Candida albicans (~ 50% cases)
C. glabrata
C. parapsilosis
C. tropicalis
C. krusei

C. auris






Some species are dimorphic or even polymorphic

Mucocutaneous infections

Vulvovaginal candidiasis
~75% women at least one episode
20% recurring


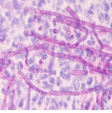
Orofaringeal candidiasis
Babies, HIV/AIDS

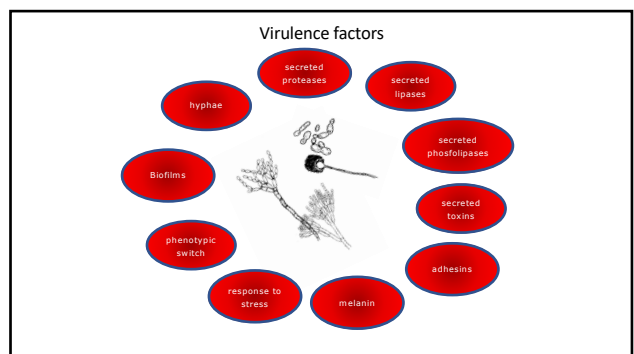
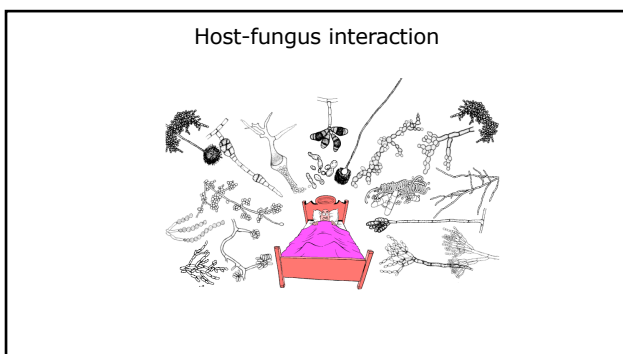
Disseminated infections

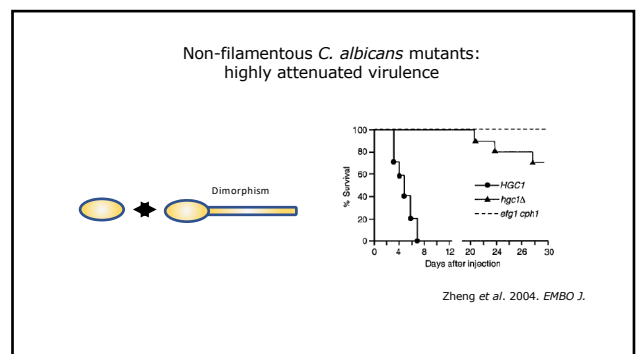
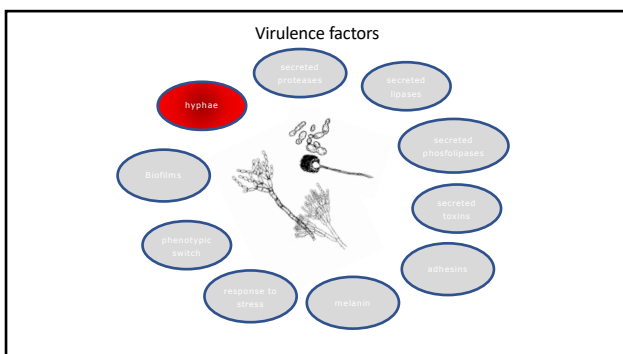
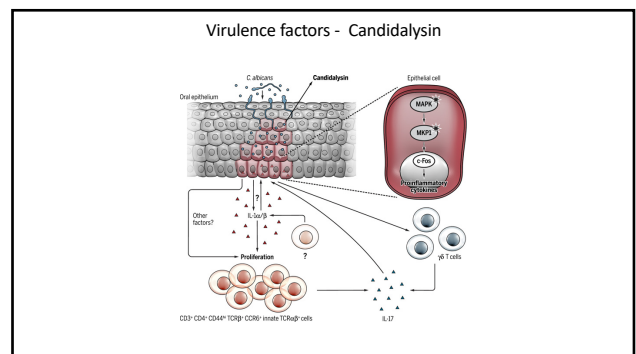
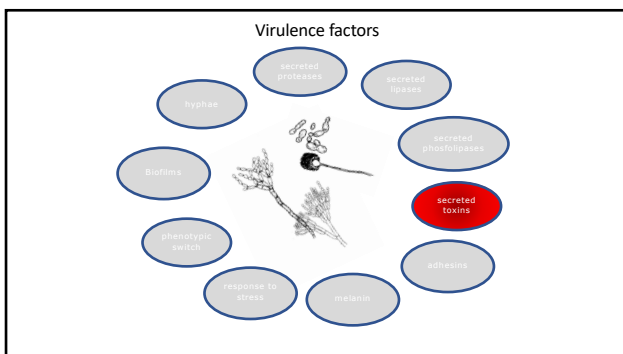
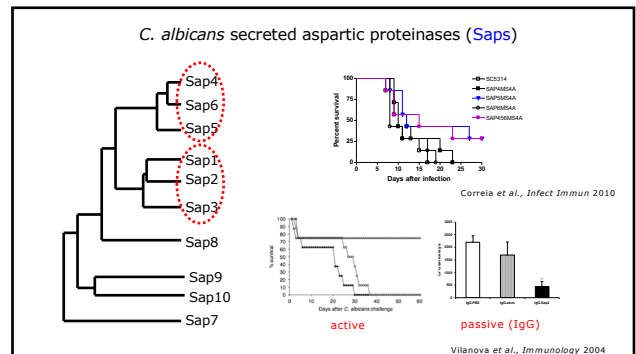
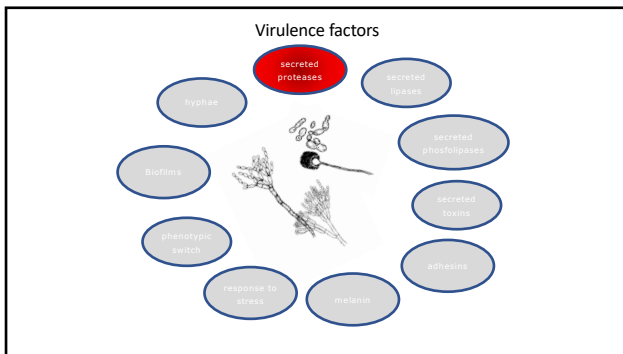
Candidemia
endogenous origin
catheters

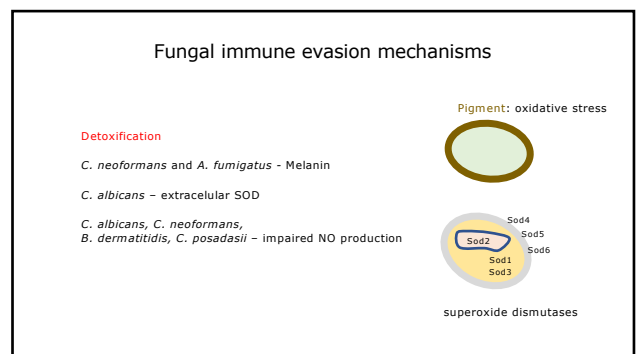
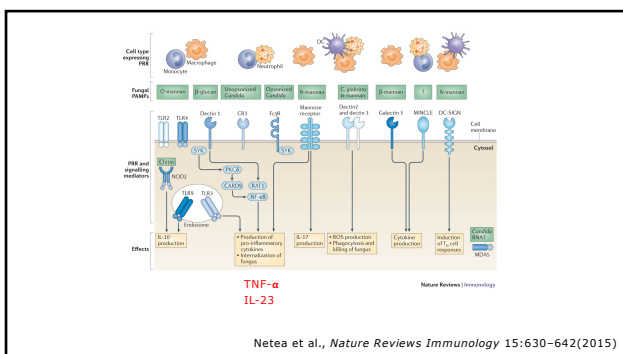
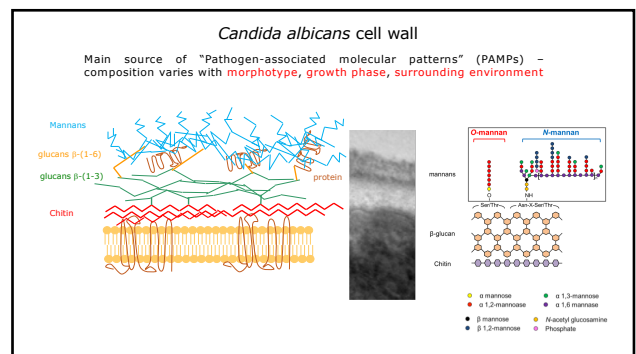
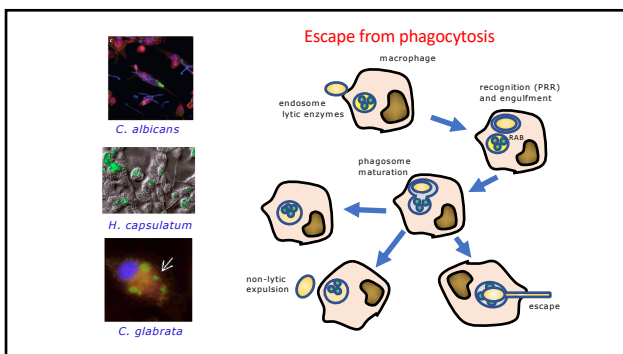
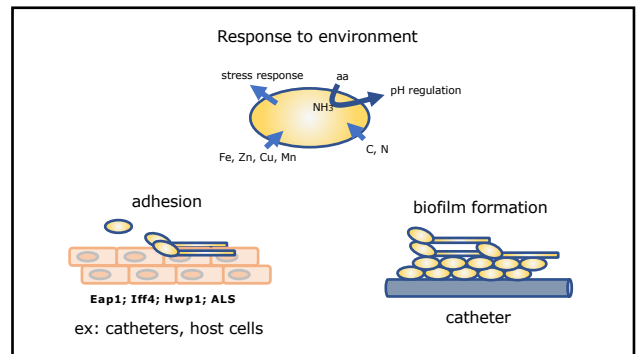
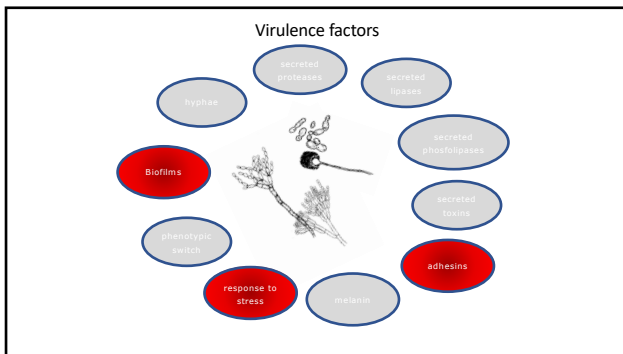
50% mortality; 50 000 deaths worldwide / annum

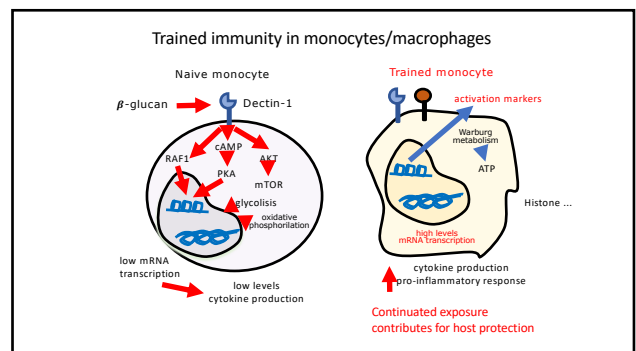
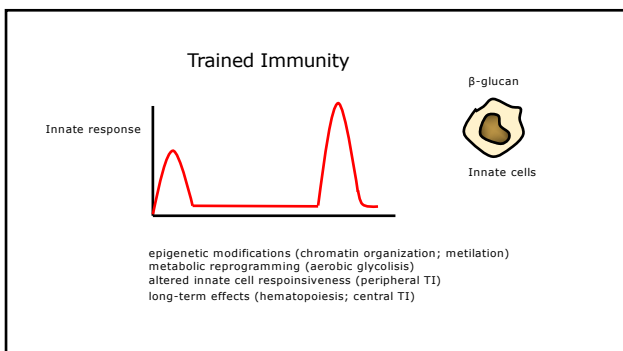
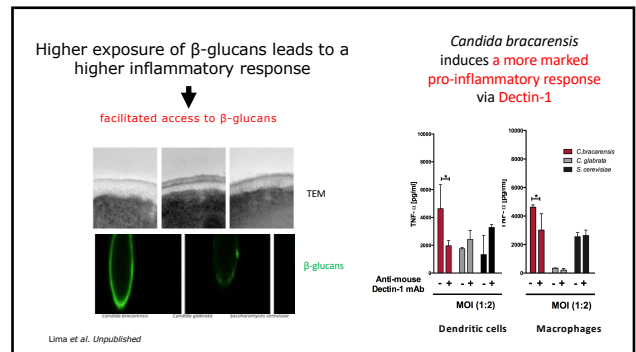
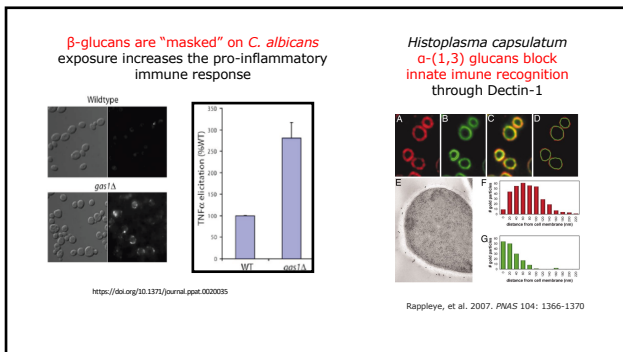



Hyper-IgE syndrome, APS-1 (APECED), IPEX, AD-CMC transplantation









Dectin-1-Mediated Production of Pro-Inflammatory Cytokines Induced by Yeast β -Glucans in Bovine Monocytes

frontiers in immunology

Ana R. V. Pedro^{1,2,3}, Tânia Lima¹, Ricardo Fido-Martins¹, Bárbara Louf⁴, Isabel C. Ramos⁴, Elisabete G. Martins^{1,5,6}, Ana R. J. Coimbra¹, António J. M. Fonseca⁷, Margarida R. G. Maia⁸, Manuel Moreno⁹ and Alexandra Cordeiro¹⁰

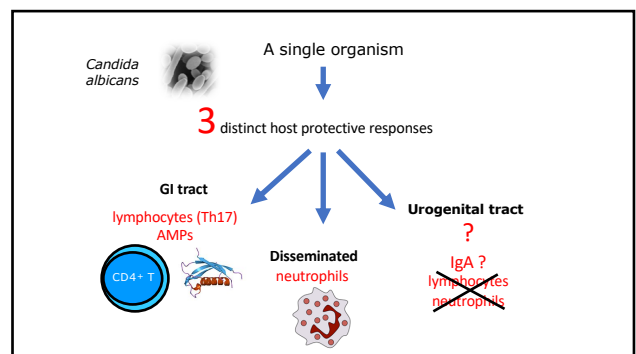
May 2021 | Volume 12 | Article 655879

Feasibility of Brewer's Spent Yeast Microcapsules as Targeted Oral Carriers

foods


Sofia E. Reis^{1,2}, Vitor J. Martins¹, Rita Bastos¹, Tânia Lima², Viviana G. Correia^{3,4}, Benedita A. Pinheiro^{3,4,5}, Lisete M. Silva¹, Angelina S. Palma^{2,4}, Paula Ferreira^{1,6}, Manuel Vilanova^{2,4,7}, Manuel A. Coimbra^{1,8} and Elisabete Coelho^{1,9}

Frontiers 2023, 12, 246.



but... crucial in mucocutaneous candidiasis

Chronic Mucocutaneous Candidiasis (CMC)
Hyper-IgE syndrome, APS-1 (APECED), IPEX



Gene defects associated to **Th17** (also **Treg**)

Mutations affecting the Th17 pathway in humans

STAT-3	} mucocutaneous
TYK2	
IL12B	
IL12RB1	
IL17F	
IL17RA	
DECTIN1	
STAT1	
AIRE	
ACT1	
IL17RC	} mucocutaneous & systemic
CARD9	

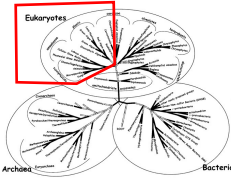
Vaccination approaches to fungal infections

Recombinant/subunit
Als-3-p: *Candida* spp
Sap-2

Conjugate
β-glucan brown algae iDT
B-1,2 mannotriose with fructose biphosphate aldolase
GXM tetanus toxoid

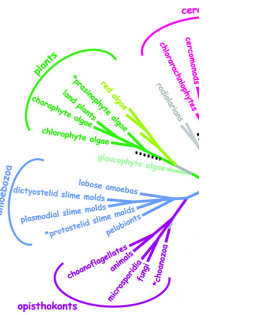
Fungal vaccines

Live-attenuated
HK *Cerevisiae*
formalin-K *immitis* spherules
attenuated strain *C. posadasii*
attenuated strain *C. neoformans*
Δ *Bad1*/*Blastomyces*
live-attenuated strain *T. verrucosum*



Fungi are phylogenetically closer to Animals than Plants

Baldal et al. 2004. in Assembling the tree of life



Antifungal therapeutic agents

amphotericin B, nistatin, natamycin (Polyenes)

fluconazole, voriconazole (Azoles)

caspofungin, micafungin (Echinocandins)

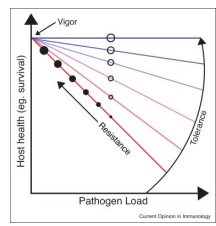
5-Fluorouracil (Pyrimidine analogues)

Mambro et al. *Front. Pharmacol.* 2019

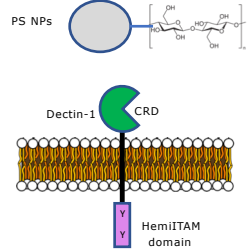
Antifungal mAbs	Source	Pathogen	Antigen
mAb C7	Mouse	<i>C. albicans</i> , <i>C. lusitanae</i> , <i>C. neoformans</i> , <i>A. fumigatus</i> , <i>S. prolificans</i>	Cell wall mannoprotein
mAb A9	Mouse	<i>A. fumigatus</i>	Cell wall glycoprotein
mAb 7B8 and 8G4	Mouse	<i>A. fumigatus</i> and <i>flavus</i>	Galactomannan of <i>A. fumigatus</i>
mAb 18B7	Mouse	<i>Cryptococcus</i> spp.	Glucuronoxylomannan
Mycograb	Human	<i>Candida</i> spp.	<i>Candida</i> HSP(90)

Mambro et al. *Front. Pharmacol.* 2019

A NP-based approach to limit inflammatory side-effects in a model of systemic candidiasis



Current Opinion in Immunology



McCarville & Ayres
Curr Opin Immunol 2018, 50: 88-93

