Fungal Allergy and Pathogenicity
Contents

XII Foreword
   M. Breitenbach, Salzburg; R. Crameri, Davos; S.B. Lehrer, New Orleans, La.

1 Introduction
   A.M. Chiu, J.N. Fink, Milwaukee, Wisc.

3 References

5 Impact of Current Genome Projects on the Study of Pathogenic and Allergenic Fungi
   M. Breitenbach, Salzburg; R. Crameri, Davos; S.B. Lehrer, New Orleans, La.

6 Candida albicans Genome Project
7 Cryptococcus neoformans Genome Project
7 Aspergillus fumigatus Genome Project
8 The Postgenomic Era
8 References

10 Fungal Aerobiology: Exposure and Measurement
   E. Levetin, W.E. Horner, Atlanta, Ga.

11 Sampling Equipment
13 Analysis
15 Patterns of Variation
19 Measurement Problems
22 Clinical Implications
24 Conclusions
25 References
28 Allergy to Basidiomycetes
 A. Helbling, K.A. Brander, Bern; W.E. Horner, Atlanta, Ga.;
 S.B. Lehrer, New Orleans, La.

28 Prevalence of Airborne Basidiospores Including Indoor Exposure
30 Prevalence of Sensitization
31 Clinical Aspects
31 Respiratory Allergy
32 Bronchial and Nasal Challenges
32 Atopic Eczema
33 Contact Dermatitis
33 Food Allergy
33 Invasive Mycosis
34 Source Materials
35 Basidiomycetes as Allergens
35 B. edulis (cèpe)
35 Calvatia spp. (Puffballs)
36 Coprinus spp. (Inky Cap)
37 Ganoderma spp.
37 Pleurotus spp. (Oyster Mushroom)
38 Psilocybe spp.
39 Cross-Reactivity
40 Molecular Biological Approaches to Basidiomycete Allergens
40 Screening of C. comatus Phage Display Library – 7 Putative Allergens
41 Cop c 1, the First C. comatus Allergen
44 Cop c 2
44 Conclusions
44 References

48 The Allergens of Cladosporium herbarum and Alternaria alternata
 M. Breitenbach, B. Simon-Nobbe, Salzburg

49 Problems with Reproducibility of Mold Extracts and the Study of Mold Allergens
51 Experience with Specific Immunotherapy in the Treatment of Mold Allergies
54 Importance of Molecular Cloning Techniques
54 Cloning, Analysis, Production and Clinical Testing of the
 Allergens of Cladosporium and Alternaria
54 Cloning Methods
57 The Major Allergen of A. alternata, Alt a 1
59 The Major Allergen, Cla h1
59 Enolase, an Important Allergen in C. herbarum and A. alternata,
 Exhibits Cross-Reactive Properties
61 Epitope Mapping of C. herbarum Enolase
62 Other Allergens
63 A. alternata
C. herbarum
Production of Highly Purified Alt a1 and A. alternata Enolase for Clinical Use
Alt a1
A. alternata Enolase
Clinical Study with Recombinant A. alternata Allergens
Discussion and Outlook
Acknowledgments
References

Molecular Cloning of Aspergillus fumigatus Allergens and Their Role in Allergic Bronchopulmonary Aspergillosis
R. Crameri, Davos

Host Defense Mechanisms and A. fumigatus-Related Diseases
A. fumigatus-Related Diseases
Diagnosis and Epidemiology of Allergic Bronchopulmonary Aspergillosis
Cloning and Molecular Characteristics of A. fumigatus Allergens
Clinical and Diagnostic Evaluation of Recombinant A. fumigatus Allergens
The Role of A. fumigatus Allergens in Allergic Bronchopulmonary Aspergillosis
Utilizing the Allergenic Repertoire of A. fumigatus Identified with Advanced Technologies
Conclusions
Acknowledgments
References

Defense Mechanisms of the Airways against Aspergillus fumigatus: Role in Invasive Aspergillosis
H.F. Kauffman, J.F.C. Tomee, Groningen

Overview of Manifestations of Aspergillosis
Nonpathogenic Saprophytic Colonization
Aspergilloma
Hypersensitivity-Induced Aspergillosis
Aspergillus Asthma
Allergic Bronchopulmonary Aspergillosis
Hypersensitivity Pneumonitis
Invasive Pulmonary Aspergillosis
Host defense against Aspergillus
Innate Defense Strategies of Airways against Fungi
The Adaptive Immunological Response
Effect of Immunosuppressing Agents on the Innate and Adaptive Defense Mechanisms
Concluding Remarks
References
114 Secreted Proteinases and Other Virulence Mechanisms of *Candida albicans*
*M. Monod*, Lausanne; *M. Borg-von Zepelin*, Göttingen

115 Site-Directed Mutagenesis and Genomics to Investigate Virulence Factors

116 Dimorphism

116 Switching System of *C. albicans*

118 Adherence

119 Secreted Hydrolases

119 Phospholipases

120 Secreted Aspartic Proteinases

121 Aspartic Proteinases in the Adherence Process

123 Aspartic Proteinases in Deep-Seated Candidiasis

124 Acknowledgment

124 References

129 Cutaneous Mycology
*T. Hawranek*, Salzburg

130 Pathogenesis of Cutaneous Fungal Infection

132 Clinical Mycology

132 Superficial Mycoses

132 Pityriasis versicolor

133 White Piedra

133 Black Piedra

134 Tinea nigra

134 Cutaneous Mycoses

134 Dermatophytosis (Ringworm, Tinea)

134 Special Clinical Patterns

134 Tinea corporis

138 Tinea inguinalis (Tinea cruris)

138 Tinea capitis

141 Tinea barbae

141 Tinea pedis (‘Athlete’s Foot’)

142 Tinea manuum

142 Onychomycosis

143 Skin and Nail Infections by Molds

143 Scytalidium Species

144 Onychomycosis Caused by *Scopulariopsis brevicaulis*

144 Onychomycosis Caused by Other Molds

144 Tinea incognito

144 ‘Superficial’ Candidiasis

145 Oral Candidiasis (Thrush)

146 Pseudomembranous Candidiasis
### Contents

**167 Toxins of Filamentous Fungi**  

- Mycotoxicosis
- Mycotoxicology
- Natural Occurrence of Mycotoxins
- History of Mycotoxins
- Classification of Mycotoxins
- Economic Impact of Mycotoxins
- Detection and Screening of Mycotoxins
- Selected Mycotoxins
  - Aflatoxins
  - Toxic Polyketides Other Than Aflatoxins
  - Ochratoxins
  - Cyclopiazonic Acid
  - Patulin
  - Penicillic Acid
  - Citrinin
  - Sterigmatocystin
  - Zearalenone
  - Fumonisins
  - Trichothecenes
  - Alternaria Toxins
- Neurotropic Mycotoxins
  - Ergot Alkaloids and Related Toxins
  - Other Neurotropic Mycotoxins
- Management of Mycotoxin Contamination
  - Preharvest Control
  - Postharvest Control
- Dietary Consideration
- Summary
- References

**207 Phylogeny and Systematics of the Fungi with Special Reference to the Ascomycota and Basidiomycota**  

- The Kingdom Mycobionta (Eumycota) or True Fungi
- Morphological Differentiation within the Kingdom Mycobionta
- Sexual Differentiation within the Kingdom Mycobionta
- Phylogenetic Relationships among the Chytridiomycota and Zygomycota
- Phylogenetic Relationships among the Ascomycota and Their Anamorphs
- Hemiascomycetes
- Protomycetes
233 Euascomycetes
234 Chaetothyriales
235 Eurotiales
237 Onygenales
239 Hypocreales
242 Ophiostomatales
242 Phyllachorales
243 Sordariales
244 Microascales
244 Dothideales
246 Pleosporales
248 Leotiales
249 Pezizales
249 Phylogenetic Relationships of the Basidiomycota and Their Anamorphs
253 Urediniomycetes
255 Cystobasidiales
255 Microbotryales
256 Uredinales
257 Ustilaginomycetes
258 Malasseziales
258 Georgefischerales
259 Microstromatales
259 Ustilaginales
260 Hymenomycetes
261 Tremellales
263 Cantharellales
264 Gomphales
264 Thelephorales
265 Polyporales
267 Hymenochaetales
268 Russulales
268 Boletales
269 Schizophyllales
270 Agaricales
272 Genotypic Identification
275 Acknowledgments
275 References
294 Notes added in proof

296 Glossary

302 Author Index

303 Subject Index
Foreword

Fungal organisms (yeasts and molds) are an increasing public health problem (Chiu and Fink) worldwide for several reasons. After transplantation surgery immunosuppressed patients frequently suffer from fungal infections which can become fatal; the AIDS pandemic, which is still on the increase, also leads to fungal infections that are difficult to treat and there is an increase in real and perceived allergic diseases which, in some developed countries, involve 20–30% of the population; a proportion of these allergies is due to inhaled fungal spores and other fungal material. Some of the older patients suffering from allergic or ‘nonallergic’ asthma are particularly prone to fungal infections of the lung. Moreover, fungal toxins (Bhatnagar et al.) still represent an important health problem both in humans and farm animals.

Exposure to fungal spores is ubiquitous and, therefore, of pivotal importance for the development of mycoses acquired via the respiratory tract. This situation has also led to increased public awareness of the importance of indoor air quality and to the emergence of aerobiology, which has established itself as a major environmental academic discipline (Levetin and Horner).

Fungal infections have led to an increasing demand for antifungal drugs. Compared to the well-known antibacterial antibiotics, these are generally less than satisfactory, because it is more difficult to combat eukaryotic than procaryotic pathogens, and severe side effects are still frequent. It is expected that fungal whole genome sequences (Breitenbach et al.), which are now being determined, will be very helpful in devising new antifungal drugs. Fungal genetics plays an increasing role in the study of clinically relevant fungi. Genome sequences will also lead the way to the discovery of new virulence factors which are important as drug targets. There are good reasons for hope, but at present no antifungal drug developed on the basis of fungal genomics is yet on the market.

Fungi are different from bacterial pathogens also because they are mostly opportunistic, that is they are present all the time in healthy individuals (for instance, on the skin), and only become dangerous in certain situations. A variety
of pathological conditions, including impaired immune function, are believed to cause host susceptibility to fungal infections. The major reason for the increase in systemic mycoses is undoubtedly related to an increased number of patients with congenital or acquired immunodeficiency. Therefore, it is important to study not only the fungal pathogens but also the host factors that contribute to fungal infectivity (Kauffman and Tomee, and Monod and Borg-von Zepelin).

Until recently, the study of fungal allergy was still in its infancy. It is no exaggeration to say that modern cDNA cloning techniques caused a major breakthrough in this field. Before the advent of allergen cloning, it was difficult, for several reasons, to identify the relevant fungal allergens unequivocally. Commercially available fungal extracts were for the most part not satisfactory for a reliable diagnosis and were not authorized for specific immune therapy (‘hyposensitization’) in many countries. This situation will improve with the advent of well-defined pure recombinant fungal allergens (Helbling et al., Breitenbach and Simon-Nobbe, and Crameri).

Nearly all major systematic groups of fungi are now known to contain allergenic and/or pathogenic species (Prillinger et al.). Among the Ascomycota, the new sequence-based phylogeny defines three large groups: the Hemiascomycetes, the Protomycetes (Archiascomycetes) and the Euascomycetes. Presently there is some debate on whether the Protomycetes are primitive Ascomycota (Archiascomycetes) or a derived group of Ascomycota with similarities to the Basidiomycota (Prillinger et al.). Until recently, some Ascomycota (Aspergillus, Alternaria, Cladosporium, Penicillium, Candida and others) were called ‘fungi imperfecti’ (Deuteromycota), but are now recognized as close relatives of ‘perfect’ Ascomycota based on molecular systematics.

The Hemiascomycete, Candida albicans, is a very important pathogen and allergen, aspects of which are treated by Monod and Borg-von Zepelin. Among the Euascomycetes, Trichophyton rubrum causes superficial skin infections (Hawranek); Histoplasma capsulatum is an intracellular parasite of the monocyte/macrophage system occasionally causing fatal infections, and Aspergillus fumigatus is a very important allergen and pathogen that is able to colonize the human lungs. Some aspects of Aspergillus infections are the topic of the chapters by Crameri, and Kauffman and Tomee. Cladosporium herbarum and Alternaria alternata (Breitenbach and Simon-Nobbe) are Euascomycetes. They are important causes worldwide of allergies. Pneumocystis carinii, an important pathogenic member of the Protomycetes, is the most common cause of lung infection in AIDS patients.

Among the major groups of the Basidiomycota, only the Uredinomycetes contain practically no known pathogens and/or allergens. Rhodotorula mucilaginosa and Rhodotorula glutinis have occasionally been isolated from patients. Interestingly, Malassezia (previously called Pityrosporum) furfur, a human
pathogen infecting the skin and hair follicles (Hawranek), is a member of the Ustilaginomycetes, a large group of plant pathogens. The most highly developed group of the Basidiomycota, the Hymenomycetes, contain a number of recently recognized important allergy-causing fungi: *Coprinus cinereus*, *Psilocybe cubensis*, and puffballs of the genus *Calvatia*, among others (Helbling et al.). Another Hymenomycete, *Cryptococcus neoformans*, is an important human pathogen causing the often fatal cryptococcosis of the lung and meningitis.

This volume clearly shows the importance of correct fungal systematics to understand the clinically relevant fungi. For this reason, we have included an extensive chapter on the new molecular fungal systematics. This chapter (Prillinger et al.) should be consulted whenever questions appear as to the correct systematic nomenclature and the older synonyms of a fungal organism. We are including a glossary because we feel that the highly specialized terminology, especially of clinical mycology and of systematic mycology, should be explained for nonspecialists.

This book addresses not only clinicians who want to learn more about clinically important fungi, but also allergologists, mycologists, biologists and lawyers concerned with the increasing number of lawsuits because of fungal spores in indoor air, which are claimed to be a major reason for ‘sick building syndrome’.

We are very grateful to Thomas Nold and the members of the team of Karger (Basel, Switzerland) for their excellent cooperation and patience during the time of collecting and editing the chapters of this book. We are also very grateful to the authors of this book who have spent many days checking and rechecking every chapter, especially to Birgit Simon-Nobbe and to Hansjörg Prillinger. Finally, we thank our families for their support and confidence in the final success of this project.

*M. Breitenbach, R. Crameri, S.B. Lehrer*