Human Fungal Pathogens

A subject collection from *Cold Spring Harbor Perspectives in Medicine*

OTHER SUBJECT COLLECTIONS FROM *COLD SPRING HARBOR PERSPECTIVES IN MEDICINE*

Tuberculosis
The Biology of Heart Disease
The Skin and Its Diseases
MYC *and the Pathway to Cancer*
Bacterial Pathogenesis
Transplantation
Cystic Fibrosis: A Trilogy of Biochemistry, Physiology, and Therapy
Hemoglobin and Its Diseases
Addiction
Parkinson's Disease
Type 1 Diabetes
Angiogenesis: Biology and Pathology
HIV: From Biology to Prevention and Treatment
The Biology of Alzheimer Disease

SUBJECT COLLECTIONS FROM *COLD SPRING HARBOR PERSPECTIVES IN BIOLOGY*

Innate Immunity and Inflammation
The Genetics and Biology of Sexual Conflict
The Origin and Evolution of Eukaryotes
Endocytosis
Mitochondria
Signaling by Receptor Tyrosine Kinases
DNA Repair, Mutagenesis, and Other Responses to DNA Damage
Cell Survival and Cell Death
Immune Tolerance
DNA Replication
Endoplasmic Reticulum
Wnt Signaling
Protein Synthesis and Translational Control
The Synapse
Extracellular Matrix Biology
Protein Homeostasis
Calcium Signaling
The Golgi
Germ Cells
The Mammary Gland as an Experimental Model
The Biology of Lipids: Trafficking, Regulation, and Function
Auxin Signaling: From Synthesis to Systems Biology

Human Fungal Pathogens

A subject collection from *Cold Spring Harbor Perspectives in Medicine*

EDITED BY

Arturo Casadevall
Albert Einstein College of Medicine of Yeshiva University

Aaron P. Mitchell
Carnegie Mellon University

Judith Berman
Tel Aviv University

Kyung J. Kwon-Chung
National Institutes of Health

John R. Perfect
Duke University Medical Center

Joseph Heitman
Duke University Medical Center

COLD SPRING HARBOR LABORATORY PRESS
Cold Spring Harbor, New York • www.cshlpress.org

Human Fungal Pathogens

A Subject Collection from *Cold Spring Harbor Perspectives in Medicine*
Articles online at www.perspectivesinmedicine.org

Printed in the United States of America

Executive Editor	Richard Sever
Managing Editor	Maria Smit
Senior Project Manager	Barbara Acosta
Permissions Administrator	Carol Brown
Production Editor	Diane Schubach
Production Manager/Cover Designer	Denise Weiss
Publisher	John Inglis

Front cover artwork: Top left: Yeast cells of *Candida parapsilosis* phagocytosed by human primary macrophages. Killed cells are in red. (Image kindly provided by Attila Gacser and Csaba Papp, University of Szeged, Hungary.) *Top middle:* Scanning electron micrograph of yeasts (green) and pseudohyphae (brown) produced in a *Candida tropicalis* calcineurin mutant strain. (Image kindly provided by Ying-Lien Chen, National Taiwan University; reprinted from *Evolution of Virulence in Eukaryotic Microbes*, 2012, with permission from Wiley/Blackwell, © 2012.) *Top right:* Scanning electron micrograph of an *Aspergillus fumigatus* ascospore. (Image provided by Bryan Hansen; originally appeared in Kwon-Chung and Sugui 2013 [*PLoS Pathog* **9:** e1003743] and is reprinted with permission from the National Institutes of Health, © 2013.) *Bottom left: Candida albicans*–infected kidney tissue stained by Periodic Acid Schiff showing hyphal invasion in the renal medulla. (Image kindly provided by Michail Lionakis, National Institute of Allergy and Infectious Diseases.) *Bottom middle:* A mature spherule of *Coccidioides posadasii* releasing endospores in the host lung. (Image reprinted from Cole et al. 2004 [*Med Mycol* **42:** 189–216], with permission from Oxford University Press, © 2004.) *Bottom right:* Four different images of a *Cryptococcus neoformans* yeast cell labeled with different reagents: red (capsule edge), green (complement protein bound to the inner capsule), and blue (cell wall stained by Calcofluor). (Image kindly provided by Oscar Zaragoza, Albert Einstein College of Medicine.)

Library of Congress Cataloging-in-Publication Data

Human fungal pathogens/edited by Arturo Casadevall, Aaron P. Mitchell, Judith Berman, Kyung J. Kwon-Chung, John R. Perfect, and Joseph Heitman.
p. ; cm.
"A subject collection from Cold Spring Harbor perspectives in medicine".
Includes bibliographical references.
Summary: "Fungal infections affect millions of individuals worldwide. They are a particular danger to immunocompromised individuals, such as those with HIV/AIDS, and invasive infections often have a mortality rate greater than 50%. This book examines our understanding of the biology of the major fungal pathogens, together with the host response, epidemiology of fungal diseases, and current treatment strategies"--Provided by publisher.
ISBN 978-1-62182-075-8 (hardcover)
I. Casadevall, Arturo, 1957- editor. II. Cold Spring Harbor perspectives in medicine.
[DNLM: 1. Mycoses--Collected Works. 2. Antifungal Agents--Collected Works. 3. Drug Resistance, Fungal--Collected Works. 4. Fungi--metabolism--Collected Works. 5. Fungi--pathogenicity--Collected Works. 6. Host-Pathogen Interactions--Collected Works. WC 450]

RC117
616.9'69061--dc23

2014020697

10 9 8 7 6 5 4 3 2 1

All World Wide Web addresses are accurate to the best of our knowledge at the time of printing.

For a complete catalog of all Cold Spring Harbor Laboratory Press publications, visit our website at www.cshlpress.org.

Contents

Preface

The study of fungal pathogens is a young field, even though humans and fungi have been closely associated throughout civilization. In fact, fungi may have ushered in the rise of mammals by contributing to the extinction of the dinosaurs and compromising reptile repopulation after an asteroid or comet struck Earth 65 million years ago. The recent emergence of the aquatic fungus *Batrachochytrium dendrobatidis* to cause global amphibian extirpation and extinction events may echo this historic catastrophe. On the other hand, fungi have contributed to society as the catalytic agents that yield beer, bread, wine, soy sauce, citric acid, and countless other products. A fungus produced the first antibiotic, penicillin, and thus saved countless lives, and many other pharmaceutical drugs are natural fungal products, including the gold standard immunosuppressive organ transplant drug cyclosporin. Fungi have further provided cornerstones in our understanding of metabolism, cell biology, genetics, and genome evolution. If the domestication of fungi began at the dawn of civilization, why has the fungal pathogenesis field been so overlooked?

Part of the answer lies in clinical manifestations. Fatal fungal infections occur primarily in patients whose defenses are impaired because of diseases such as HIV/AIDS, rare genetic predispositions like chronic granulomatous disease, medical interventions such as cancer chemotherapy, implanted devices (e.g., artificial joints, heart valves, catheters) and organ transplantation, or developmental immaturity as a consequence of premature birth. The frequency of patients with such conditions has skyrocketed in the recent past because of the HIV/AIDS epidemic, the war on cancer, and dramatic advances in medical technology. Other types of frequent fungal infections among the global population include the superficial infections caused by dermatophytes (e.g., athlete's foot), *Malassezia* species (eczema and dandruff), and *Candida albicans*, which causes vaginal infections and thrush. In aggregate, these species cause *billions* of infections each year.

Another part of the answer lies in the availability of scientific tools. Fungal pathogens at first seemed to be biological eccentrics, with distinct features of their growth and life cycles that presented daunting challenges to scientists trained on model organisms such as the reluctantly pathogenic model yeast *Saccharomyces cerevisiae*. But eccentricity is novelty when unraveled, and it can provide a unique understanding of pathogenicity as well as new directions for the development of antimicrobials or vaccines. Put another way, a central tenet of *The Art of War* by Sun Tzu is "If you know the enemy and know yourself, you need not fear the result of a hundred battles. If you know yourself but not the enemy, for every victory gained you will also suffer a defeat. If you know neither the enemy nor yourself, you will succumb in every battle." Thus, to make progress in diagnosing, treating, and preventing human infections caused by fungi, we must "know the enemies." We are privileged to have witnessed an explosion in knowledge of human fungal pathogens, driven by the development of genetic, genomic, and molecular tools specific to these microbial pathogens, as well as the sophisticated understanding of model fungi that blossomed over the past two decades and provides a conceptual framework.

The final part of the answer lies in a consideration of the evolution of human fungal pathogens within the broader fungal kingdom and casting this into a phylogenetic and genomic framework. In contrast to many common bacterial and viral microbial pathogens that are communicable, many fungal pathogens are environmental organisms (such as *Cryptococcus neoformans*) in which each encounter with the host might be considered accidental. This is cast against another group of human fungal pathogens that are either commensals that can emerge to cause infection (such as

Candida albicans) or microbes that are directly transmitted human to human (such as *Pneumocystis*). Thus, some human fungal pathogens might be viewed as "accidental" pathogens, whereas others are evolved pathogens. There are an estimated 2 to 5 million species of fungi on Earth, of which only a fraction cause human infections. Pathogenesis has evolved repeatedly and independently throughout the fungal tree of life, and yet we also find closely aligned complexes of pathogenic species. There are also unique groups of fungal species specialized to live on human skin and in other niches in the body, and our understanding of their interactions with others in the microbiome is still in its infancy, but what we do know is covered in several chapters herein.

In editing this book, we strove to take advantage of the youth of our field by providing a comprehensive set of perspectives. We begin with a set of chapters that capture the overarching principles of fungal biology, genetics, and genomics. We then present a series of chapters on the defense mechanisms that protect most of us from infection, the virulence mechanisms that allow infections to occur, and the state of the art in therapeutic strategies. Finally, we have chapters on individual fungal pathogens that illustrate how those overarching principles apply and also point out many of the biological eccentricities of today that will lead to the novel insights and therapeutics of tomorrow.

We are indebted to Richard Sever of Cold Spring Harbor Laboratory Press who conceived this effort and enlisted us as editors. We are grateful to Melissa Palmer for her efforts to keep us each on track and to Barbara Acosta, our coordinating project manager at Cold Spring Harbor Laboratory Press, without whom this effort would not have been realized. We are grateful to our families for their forbearance, and to our authors for sharing their visions with us. Finally, as with any publication, the ultimate impact and success will lie with you, our readers. We invite you to explore the realm of the fungal kingdom that specifically intersects with our own by causing frequent global infections and to communicate to us your thoughts on this effort. It is our hope that this effort will inform and spur your own investigations and that thereby a future edition of this book might not be necessary.

Arturo Casadevall
Aaron P. Mitchell
Judith Berman
Kyung J. Kwon-chung
John R. Perfect
Joseph Heitman