Drug Resistant Fungi

by **David Perlin**

The crisis of antimicrobial drug resistance and the emergence of "superbugs" threaten human health. We hear it all the time. A simple infection that should be easily treated with antibiotics goes so badly awry that a life-threatening situation arises. In an instant, decades of work invested to develop an antibacterial or antiviral agent can be rendered useless through simple genetic selection. As we rely upon antimicrobial agents to aid against infection for a wide array of advanced medical procedures that leave patients highly susceptible to infection, we are in a vulnerable state. The emergence of drug resistance may be the single most important factor that threatens advanced health care delivery and adds hugely to its costs. We know about bacterial and viral infections...but how much is known about invasive fungal infections?

In fact, drug resistant fungi cause both acute and chronic infections with high morbidity and mortality. Yet, they remain an under-recognized threat to human health. Most serious fungal infections are a consequence of underlying health problems such as AIDS, cancer, cystic fibrosis and transplantation. Invasive *Candida* infections are the fourth leading cause of hospital-acquired blood stream infections, and they are associated with a high mortality (>40%). *Candida* and *Aspergillus* species cause a majority of serious infections in non-HIV patients. Early diagnosis and aggressive antifungal therapy are critical for a successful clinical outcome. Yet treatment options for invasive fungal infections are limited, as there are few chemical classes represented by polyenes, triazoles and the newest class, echinocandins.

However, it is not just immunosuppressed patients who cope with invasive fungal infectious, but otherwise healthy patients can develop chronic diseases such as aspergillosis, severe asthma with fungal sensitization, and other inflammatory and

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debilitating lung diseases. The problem is that these infections are difficult to diagnose and often require therapy in the absence of positive identification of an infecting organism. Without therapy, these patients face a bleak future. If one superimposes drug resistance and rapid dispersal in the air, there is a perfect storm that threatens human health. The Perlin lab has spent the last two decades understanding the emergence of antifungal drug resistance, elucidating molecular details of the resistance mechanisms, and developing strategies to counter resistance.

How big is the problem?

Fungal infections affect tens of millions of people worldwide each year and result in more than 1.3 million deaths. The overall annual incidence of acute invasive aspergillosis among the immunosuppressed patient population may be as high as one in ten. Mortality is very high and drug resistance exacerbates it. Patients with multi-azole resistant invasive aspergillosis have an 88% mortality. The etiologic agent, *Aspergillus fumigatus*, is a soil-borne fungus that is highly prevalent in the air and transmitted globally through airborne conidia. Every day we inhale hundreds, sometimes thousands, of spores. In most cases, the immune system eliminates the invading spores. However, in the unfortunate minority, the spores germinate and cause disease. Aggressive therapy with triazole antifungal agents is critical for these patients. Yet, as has been seen so many times before, the infecting strains either acquire resistance during therapy or strains already in the environment that are drug resistant are selected during therapy. Either way, the results can be catastrophic to the patient.

Manchester connection

To more directly engage the emerging problem of drug resistance in *Aspergillus*, I just completed a three-year term as a visiting professor with Dr. David Denning, Director of the National Aspergillosis Center in Manchester, United Kingdom, where drug resistance approaches 20%. Our collaborative studies resulted in an improved understanding of the molecular basis for drug resistance and the development of new tools to better identify infection and the presence of resistant organisms. In one highly cited recent study, we collectively showed that molecular amplification techniques could detect invasive aspergillosis, when conventional culture techniques failed. In an extraordinary and frightening finding, we also discovered that more than 50% of patients were harboring drug resistant organisms. These findings have major implications for clinical practice and may help explain the modest overall response of patients to antifungal therapy. A better understanding of resistance mechanisms is needed to identify resistant strains at an earlier stage and to assess more effective intervention strategies.

A new antifungal drug class…but a familiar story

The echinocandin drugs are the newest antifungal drugs to enter the market. They are lipopeptides that inhibit glucan synthase, which is responsible for the biosynthesis of β-1, 3-D- glucan, a critical building block of fungal cell walls. They are very safe drugs that are highly active on *Candida* and *Aspergillus* species. However, the expanding use of echinocandin drugs has resulted in growing resistance among *Candida* species, which threatens this new drug class. In some susceptible species, resistance has increased more than 12-fold over the past half decade. Our lab has been pivotal in understanding the molecular basis for resistance, developing guidelines for therapy and diagnosis, and exploring innovative therapeutic dosing strategies to overcome resistance. We were the first to describe the now textbook *fks* mechanism for drug resistance centered on mutations in the *FKS* genes that encode the echinocandin target. Such mutations greatly alter the susceptibility of the target enzyme to drug rendering some fungal cells nearly invisible to drug action. Pfizer established the Perlin lab in 2006 as a global reference center for echinocandin resistance. We have published more than 40 articles on echinocandin resistance in the past 5 years.

Perspective

Fungal infections threaten human health in both overt and stealthy ways. We need better tools to diagnose infections early in the disease process and monitor the emergence of drug resistance. Most importantly, we need better strategies to protect existing drugs and develop new classes of effective drugs to treat resistant infections. Our time to act is now, and the Perlin lab will continue to make overcoming drug resistance a priority. ■

David Perlin is Executive Director of the Public Health Research Institute at New Jersey Medical School (NJMS), a leading infectious diseases research organization. An expert in drug resistant fungal infections and rapid diagnosis of opportunistic pathogens in high-risk patients, he is also a professor of microbiology and molecular genetics at NJMS, Director of the UMDNJ Regional Biocontainment Laboratory, a nationally-designated biodefense center, and a Fellow of the New York Academy of Sciences. His laboratory is supported by grants from the NIH, pharmaceutical and biotech sectors. He earned a PhD from Cornell University and pursued post-doctoral studies at the Yale University School of Medicine and the University of Rochester School of Medicine and Dentistry. He joined PHRI in 1985. Dr. Perlin regularly lectures on issues of global infectious diseases, drug resistance, and hospital-acquired infections.

Tuberculosis + Helminths = Trouble^2

by **William G. Gause and Padmini Salgame**

Researchers have long studied the impact of *Mycobacterium tuberculosis* infection on the host immune response in the setting of a single infection and in the absence of any chronic disease. However, in the real world, *M. tuberculosis*-infected humans are co-infected with other bacteria, viruses and parasites or have underlying chronic disease, all of which have the potential to influence the development of host immunity against tuberculosis. Indeed, co-infection is a common occurrence in humans in the developing world, underscoring the importance of understanding how the immune response and host resistance against *M. tuberculosis* infection is modulated in co-infected hosts. While it has long been recognized that HIV co-infection is a significant exogenous contributor to increased susceptibility to tuberculosis, there is now growing interest in investigating whether co-infection with parasitic worms is also an acquired risk factor for tuberculosis.

Global tuberculosis (TB) control remains a major public health challenge. In 2010, there were 8.8 million incident cases and 1.4 million deaths from TB. The developing regions of sub-Saharan Africa, Asia, and the Americas contribute to a significant proportion of the TB cases worldwide. Coincidentally, over 300 million people in these developing regions are also infected with one or more helminths. Although helminths are not usually fatal, chronic infection often results in markedly impaired physical and cognitive development and function and as yet there are no effective helminth vaccines. Because relatively little research has previously been conducted on helminths, they are categorized as neglected tropical diseases. Besides the geographic overlap, a hallmark of helminthic infections, both in experimental models and human infection, is the generation of profound T helper (Th)-2 and T regulatory cell responses, immune responses that are protective against helminths but obstructive to the development of Th1 cells necessary for protection against TB. In humans, co-infection with intestinal nematodes, such as *Ascaris lumbricoides* hookworms *(Necator and Ancylostoma)* and *Strongyloides stercoralis*, that transit through the lungs as part of their life cycle, has the potential to alter the lung