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Some fungi in the air[☆]

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“The demons don’t like fresh air. What they like best is if you stay in bed with cold feet”, said the Swedish film artist Ingmar Bergman. If that applies to demons named *Aspergillus fumigatus* who tend to take up residence in the lung of immunocompromised individuals where they encounter hypoxic conditions is still a subject of controversies. One thing we have to keep in mind at any cost when studying *Aspergillus*/host interactions is that the latter takes place in a system far from so-called physiological conditions. Filamentous fungi exist since about a billion years ago; as a consequence, our present immune system had plenty of time through evolution to cut their teeth with fungal specificities, considered by some as the main selective pressure on the primitive immune system [2,3]. Thus fungal diseases are quite uncommon in the immunocompetent subject. At least this was the *status quo* half a century ago, when *Aspergillus fumigatus* had settled for living mainly in soil and on decaying organic material, excelling not in sophisticated virulence but rather in stress tolerance and flexibility vis-à-vis the changing temperature and oxygen conditions in a compost heap. Then human modern medicine started to switch organs between individuals, to refill hematopoietic stem cell reserves and to muzzle the immune system in order to protect the spare organs. And suddenly some spores arriving continuously in the lung alveoli, where they were usually quickly dealt with by alveolar macrophages and neutrophils, encountered much less resistance and started to happily spread their hyphae in the direction of underlying blood vessels [4,5]. In other words, *A. fumigatus* is an opportunistic human pathogen and its behavior facing the new playground risks to be rather random and based on outdoor-survival techniques than evolution-shaped. For example, why would someone invest precious metabolites in thickening a cell wall when oxygen becomes rare instead of shutting down consequently all useless expenditures [1]? Hard times for those who try to decipher the interplay of host microenvironment and pathogens, as the fragile equilibrium between efficient clearance and suicidal overreaction established by a functional immune system already collapsed.

Biosketch — Robert A. Cramer

Robert A. Cramer reunites science, art and literature in his career: he obtained both a bachelor of Arts and of Biology at the Lawrence University of Appleton (US) in 1999 followed by a Master of Science in 2001 and a Doctor grade in Philosophy in 2004 under Dr.

[☆]Article highlight of “Hypoxia enhances innate immune activation to *Aspergillus fumigatus* through cell wall modulation” by Kelly M. Shepardson et al. [1].

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Christopher Lawrence at the Colorado State University (US). Pursuing his scientific path, Robert Cramer obtained a post-doctoral fellowship in the medical center of Duke University (US) in the laboratories of Dr. John Perfect and Dr. William Steinbach. During the period from 2007 to 2012 he worked as an assistant professor at the Montana State University (US) department of Immunology and Infectious Diseases. Since 2012 he is an assistant professor at the department of Microbiology and Immunology at the Geisel School of Medicine Dartmouth (US).

Interview with Robert A. Cramer

What triggered your interest in *Aspergillus fumigatus*?

I became interested in fungi as a first year graduate student working on the plant fungal pathogen *Fusarium oxysporum*. I was fascinated with microbiology as an undergraduate and I found fungi to be very interesting from a morphological and evolutionary perspective as eukaryotic pathogens. When I completed my PhD, I wanted to continue exploring mechanisms of fungal pathogenesis and felt that there was a need for a greater understanding of human fungal pathogenesis mechanisms. I wanted to continue studying molds, and as *A. fumigatus* is the most common mold associated with human infections, I sought a post-doctoral fellowship to study *A. fumigatus*. I have now been studying this so called menacing mold as my primary research focus for about 10 years.

What was your first reaction when you faced the results? Did you expect them?

The increase in cell wall material and its altered exposure in hypoxia were unexpected. We knew from some previous work in *Saccharomyces* and *Candida albicans* that cell wall protein abundance could change in response to oxygen, but we did not anticipate the major changes we observed in the carbohydrate composition under low oxygen conditions. So our first reaction was, wow, this really is a significant change in a major fungal pathogen associated molecular pattern in an infection relevant condition that we then continued to explore in collaboration with Dr. Tobias Hohl's laboratory.

How will the project go on?

From the fungal perspective, we are interested in the underlying molecular mechanisms by which oxygen affects fungal cell wall biosynthesis and ultimately pathogenesis. From the host perspective, we are interested in discovering the clinical/disease ramifications of the increase innate immune activation in response to hypoxia-exposed fungi. Determining the underlying mechanisms and their ultimate ramifications will help drive new therapeutic options for these infections.

What is the take-home message of the article?

From my perspective, the main take home message is that infection site microenvironments, or host pathogen interactions if you will, are incredibly dynamic. Small changes in the infection microenvironment can have major significance for pathogen's so called "virulence" and the host's subsequent defense response. How these changes interact and manifest themselves in terms of disease are important lines of future and ongoing inquiry to develop novel therapeutic strategies for these too often lethal infections. While drug-centric approaches to infectious disease are likely to remain our primary means of combating these infections for the foreseeable future, manipulation of the infection site microenvironment to alter pathogen/host metabolism should not be overlooked.

What advice would you give to the young next- generation scientists?

Work hard. But it is much easier to work hard when you are passionate about what you are doing. Science is challenging, we often deal with "failure" on a daily basis, and it is that passion that leads to persistence and success. I also think balance in one's life is important for maintaining and enhancing our passion and drive. It (balance) can also soften the "blow" of a bad day in the laboratory, at least for a bit ☺.

What is your favourite hang-out method after a tough day at the lab?

Fly Fishing and playing with my kids.

In your opinion, what are the three most important (scientific) discoveries of the last decade?

- The Microbiome — both from the human health perspective but from a global ecological perspective as well.
- The confirmation of the existence of dark matter
- The Human Genome Project

If you could travel back in time — what historical personality would you like to meet and what scientific discovery to assist to?

On a "great person" level, probably George Washington (first USA president). From a scientific perspective, Louis Pasteur and his microbiological discoveries including fermentation. On a human level, Jesus of Nazareth.

If you could travel forth in time — what eventual invention would you like to check out?

There are many issues facing our global society that are going to require many innovative inventions, some will most certainly come from science and technology, but others will come from philosophy and the social sciences. It is hard to pick one “needed” invention that I would like to check out.

Biosketch — Tobias M. Hohl

Tobias M. Hohl received a BS in biochemistry and molecular biology from Duke University (US) and obtained M.D. and Ph.D. degrees from the Tri-Institutional M.D.-Ph.D. Program at Cornell University Medical College (US), Memorial-Sloan-Kettering Cancer Center (MSKCC) (US), and Rockefeller University (US). He completed his graduate thesis in the laboratory of Jim Rothman, an internal medicine residency at New York Presbyterian Hospital (US), and an infectious disease fellowship at MSKCC. As a research fellow, he began to work on fungal immunology under the mentorship of Eric Pamer at MSKCC before establishing an independent laboratory at the Fred Hutchinson Cancer Research Center (US) in 2009, where he is also an adjunct assistant professor in Microbiology.

Interview with Tobias M. Hohl**What triggered your interest in *Aspergillus fumigatus*?**

In 2003, I started to train as an infectious diseases fellow in a cancer hospital (Memorial Sloan-Kettering) and treated bone marrow transplant patients with invasive aspergillosis. I became interested in aspergillosis because its treatment was difficult, the patients did poorly,

and I realized that we did not understand fundamental questions about the immune response and host immunity to the fungus. I decided then to join Eric Pamer's lab as a post-doctoral fellow and began to work on how the fungus is recognized by the respiratory immune system.

What was your first reaction when you faced the results? Did you expect them?

The project was a fantastic collaboration between Robb Cramer and me. He is a classically trained fungal geneticist and identified hypoxia as an important tissue microenvironment during pulmonary aspergillosis. The collaboration started after the 2011 Gordon research Conference meeting when we discovered that we had the combined expertise to understand how pulmonary hypoxia affects fungal growth and potentially alters host responses. The collaboration worked very well because we each brought complementary expertise to the project. I should also mention that we got a nice assist from Jean-Paul Latgé who worked on the carbohydrate composition of hypoxic- and normoxic-grown hyphae.

How will the project go on?

Robb and I are continuing to collaborate. He is focusing on understanding how hypoxia regulates immune responses at a mechanistic level. I have gone on to develop fluorescence-based methods to quantify fungal killing in the lung. We believe that these approaches can be combined to understand hypoxia's effect on the outcome of host cell — *Aspergillus* responses on a molecular level.

What is the take-home message of the article?

An important message is that hosts and pathogens induce changes in tissue environments, which turn are central to understanding the outcome of infections. Physical parameters of the infection microenvironment, such as hypoxia, are difficult to model, yet play an important role in infectious outcomes and the development of immunity.

What advice would you give to the young next- generation scientists?

Do what you love doing and seek out a mentor.

What is your favourite hang-out method after a tough day at the lab?

Playing with my two children and reading a good book.

In your opinion, what are the three most important (scientific) discoveries of the last decade?

Communication and dissemination of science through the Internet, in effect social networking and flow of information.

Though it stretches far beyond the last decade, I think that vaccination and antibiotics have revolutionized human health and will remain at the forefront of medicine.

Nanotechnology and advances in materials sciences.

If you could travel back in time — what historical personality would you like to meet and what scientific discovery to assist to?

I am fascinated by the writings and influence of Frances Crick and Sydney Brenner — literally stepping into the cast of the 8th Day of Creation and experiencing the early days in the molecular biology revolution would be fantastic.

If you could travel forth in time — what eventual invention would you like to check out?

Time and space travel — would be a blast!

Seeing how genomics and proteomics are integrated into and drive future innovation in medicine.

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Background

- The mold *A. fumigatus* is a saprophyte that grows in soil and on decaying plant material [4]. The mycelium forms conidiophores releasing spores dispersed through the air and inhaled by humans [2]
- In highly immunocompromised persons (patients treated for blood malignancies, transplant recipients, AIDS patients and persons under corticosteroid treatment *A. fumigatus* can cause invasive aspergillosis with very high mortality rates [5]
- Dectin-1 is besides TLR2 and TLR4 the major receptor for fungal pathogen associated molecular patterns (PAMPs), recognizing the β -1-3-glucan of the fungal cell wall

In A Nutshell

- *In vitro* exposure of *A. fumigatus* to hypoxia induces the thickening of the cell wall and the decrease of the hyphal diameter
- This process correlates with changes in the proportional amounts of cell wall compounds, notably with the increased presence of β -glucan on its surface. *In vivo*, high levels of exposed β -glucan colocalize with hypoxic micro-environments in the lung of infected corticosteroid mice
- Hyphae grown under hypoxic conditions stimulate higher TNF and CXCL2 release and greater hyphal damage by murine macrophages and neutrophils *in vitro*, depending partially on the β -glucan receptor dectin-1