Microbial Biochemistry and Physiology (until 2015)

We investigate the pathogenesis and adaptation of fungal pathogens.

- Nutrient acquisition and metabolism of pathogenic fungi during infection
- *In vivo* real-time imaging of fungal infections in murine model systems
- Secondary metabolites of *Aspergillus terreus*

In recent years, life-threatening fungal infections have become more important. This is mainly due to increasing numbers in patients under immunosuppressive regimens. Unfortunately, the scientific knowledge on fungal infections, as well as therapeutic strategies are limited.

For this reason, we are investigating the potential of pathogenic fungi to acquire and metabolise host-derived nutrients. In this research, we are looking for metabolic processes common in different fungal species, but also on pathways specific for selected pathogens to resemble the great variety of possible host-pathogen interactions. Since nutrient acquisition is essential for successful host colonisation, the aim of these studies is the definition of new antimycotic targets.

Studies of the infection process frequently use conventional infection models that can only provide snapshots of the infection from which then the broader picture of the disease progression has to be assembled. Therefore, we are developing *in vivo* imaging systems that allow the visualisation of disease progression in individual living animals in temporal and spatial resolution. This enables the monitoring of antimycotic therapy efficacy under *in vivo* conditions and permits the detection of cryptic niches of infection that may be overlooked by histological analyses.

Last, but not least, using *Aspergillus terreus* as a model organism, we investigate the impact of secondary metabolites on fungal pathogenesis and environmental adaptation. Selected metabolites are tested for their biologic activities to draw conclusions on the connection between natural product synthesis and environmental factors.
Recognition, uptake and utilisation of nutrient sources are an essential prerequisite for all living organisms. Thus, pathogenic microorganisms must not only be able to escape the host immune response, but also to acquire nutrients from the host environment.

In our studies, we investigate the metabolic physiology of pathogenic fungi to elucidate the specific impact of nutritional pathways for the infection process. Thereby, we focus on both catabolic processes and anabolism. Examples are the utilisation of propionyl-CoA generating nutrient sources, the impact of the glyoxylate cycle in virulence and the de novo synthesis of the amino acid lysine. Since essential metabolic pathways provide suitable targets for new antimycotics, we do not limit these investigations to a single fungal species. Comparisons of different species frequently show that a variety of different solutions has evolved to solve a specific metabolic problem.
To study virulence, the impact of specific immune components and the investigation of the efficacy of antifungal drug treatments and murine infection models are frequently applied. In conventional studies selected animals are removed from the experiments and analysed at distinct time points, which only provides a snapshot of the infection process. In contrast, *in vivo* imaging makes it possible to follow the establishment of infection and disease progression in individual animals in temporal and spatial resolution. This allows to identify cryptic sites of infection and enables the visualisation of drug efficacy in spatial resolution and in real-time.

Especially luminescence based imaging systems possess an excellent signal to noise ratio for *in vivo* investigations. Therefore, we are establishing bioluminescent reporter strains of different fungal species. To generate these strains, we construct synthetic reporter genes that are adapted to the specific target organism and are cloned under the control of strong promoters. Currently, we are focussing on the generation of bioluminescent Aspergilli, *Candida* species and different *Cryptococcus neoformans* serotypes.

Interactions with immune cells

Cells of the innate immune system are of special importance for the recognition, control and elimination of fungal pathogens. Thus, patients with attenuated immune response are of special risk to acquire life-threatening fungal infections. Unfortunately, the impact of the different components of the immune system has only been partially understood. Additionally, the impact of different immune cells may differ from pathogen to pathogen and even closely related fungal species may have developed independent mechanisms to escape the immune response.

We focus our work especially on the differences in immune cell interaction by *Aspergillus fumigatus* and *Aspergillus terreus*. We showed that both species interact differently with alveolar macrophages, which form a first line of defence against fungal spores. *A. fumigatus* inhibits acidification of phagolysosomes and rapidly escapes macrophages by elongating hyphae. In contrast, *A. terreus* does not inhibit this acidification, but persists within the phagolysosome for days or weeks. This difference is mainly based on the pigments present in the spores that are of different origin in both species. Since *A. terreus* infections are much more frequently associated with disseminations, we are currently investigating the possibility of using immune cells as a vehicle for dissemination within the host.
Aspergillus fumigatus escape from macrophages

Secondary metabolites from A. terreus

Aspergillus terreus is known for its ability to produce the primary metabolite itaconic acid and the secondary metabolite lovastatin. While itaconic acid is an interesting intermediate for several chemical processes, lovastatin is used for the reduction of cholesterol levels in patients by inhibiting the HMG-CoA reductase. Interestingly, genome analyses have shown that A. terreus possesses a much higher potential of producing natural products than has been identified so far.

In our studies, we try to activate selected gene clusters from A. terreus. The aim is the identification of novel metabolites and the characterisation of their biologic activities. A special attention is given to the backwards correlation of the biologic activities and the environmental conditions leading to its production. Investigation of gene expression under natural conditions additionally involves the generation of reporter strains that indicate the expression of the cluster under selected conditions. Due to these studies we have recently been able to provide a correlation between the production of the natural product terrein and plant interactions. Plant derived media are strong inducers for terrein production, whereby terrein can harm the surfaces of fruits and suppresses growth of plant seedlings. Thus, terrein production seems to have evolved as an adaptation to life within the rhizospheres. More detailed characterisations and other metabolites are currently under investigation.

Terrein-induced lesions on banana skin surface
Publications

2015


2014


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Cruz AH, Brock M, Zambuzzi-Carvalho PF, Santos-Silva BK, Trojan RF, Góes AM, Soares CM, Pereira M (2011) Phosphorylation is the major mechanism regulating isocitrate lyase activity in *Paracoccidioides brasiliensis* yeast cells. *FEBS J* 278(13), 2318-2332. Details PubMed


