Progress in the fight against harmful fungi

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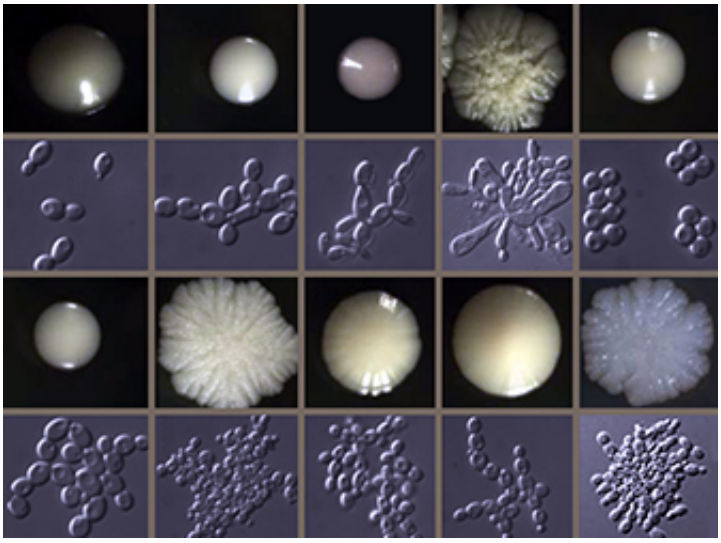

Progress in the fight against harmful fungi

A group of researchers at the Max F. Perutz Laboratories has created one of the three world's largest gene libraries for the Candida glabrata yeast, which is harmful to humans. Molecular analysis of the Candida glabrata fungus mutations led to the discovery of 28 new genes that are partly responsible for the yeast's tolerance of common drugs.

Infectious diseases caused by fungi, viruses, bacteria and parasites represent the world's number one cause of death. A few dozen types of harmful fungi claim more than 1.5 million human lives every year. Especially people with a severely weakened immune system are at particular risk of infections with yeasts of the Candida species, with

invasive infections being fatal in around 40 per cent of cases. Medications are expensive, and fungi are increasingly developing resistance.

The working group led by Karl Kuchler at the Max F. Perutz Laboratories (MFPL) - a research and training centre run jointly between the University of Vienna and the Medical University of Vienna at the Vienna Biocenter Campus - coordinated an international study cooperation aimed at researching new tolerance and virulence genes in Candida glabrata. During this process, genetic methods were used to generate one of the three world's largest libraries of "knock-out fungi". More than 600 fungus mutations were created from which a single gene was specifically removed.

As now published in the highly respected journal *PLoS Pathogens*, the molecular analysis of the Candida glabrata fungus mutations revealed 28 new genes that confer anti-fungal tolerance, especially to the popular drug Caspofungin. The study, in which the coordinators in Vienna also collaborated with groups from the Johns Hopkins University, the Institut Pasteur in Paris, the Fraunhofer Institute in Stuttgart, the Imperial College in London and the Genomics Institute in Barcelona, also identified new intra-cellular stress sensors and signal transmitters in Candida glabrata. Removing these characteristics genetically leads to marked sensitivity to all of the anti-fungal medications currently used in clinical practice - including Caspofungin.

"Since genetically removing these virulence factors from Candida glabrata patient isolates markedly reduces their virulence as well as dramatically increases the fungal pathogens' sensitivity to medications, these signal transmitters are the best points of attack for the development of new and highly effective anti-fungal therapies," says Karl Kuchler from the MFPL. "These findings represent a new milestone in the discovery and characterisation of Candida glabrata resistance genes,

laying the foundations for the development of new anti-fungal medications. This means that, in future, it will be possible to treat the often fatal invasive infections with pathogenic fungi in a more targeted and efficient manner."

Worldwide, more than Euro 8 billion is spent worldwide on anti-fungal medications, and the overall costs of treating the conditions caused by pathogenic fungi exceed hundreds of billions worldwide. The second-most common Candida fungus harmful to humans, Candida glabrata, is a major clinical problem since it has sophisticated natural tolerance and can demonstrate resistance triggered by anti-fungal therapy to the most important medications. As a result, infections with Candida glabrata need to be treated with very expensive drugs such as Caspofungin. Caspofungin blocks the biogenesis of components of the carbohydrate-rich cell wall, which is only found in fungi. The treatment of Candida glabrata, however, is becoming increasingly difficult due to the fact that anti-fungal resistance is common, the costs of Caspofungin are very high and because the frequency of infections with Candida glabrata has increased tremendously.

More information: "Systematic Phenotyping of a Large-Scale Candida glabrata Deletion Collection Reveals Novel Antifungal Tolerance Genes" – Tobias Schwarzmüller, Biao Ma, Ekkehard Hiller, Fabian Istel, Michael Tscherner, Sascha Brunke, Lauren Ames, Arnaud Firon, Brian Green, Vitor Cabral, Marina Marcet-Houben, Ilse D. Jacobsen, Jessica Quintin, Katja Seider, Ingrid Frohner, Walter Glaser, Helmut Jungwirth, Sophie Bachellier-Bassi, Murielle Chauvel, Ute Zeidler, Dominique Ferrandon, Toni Gabaldo, Bernhard Hube, Christophe d'Enfert, Steffen Rupp, Brendan Cormack, Ken Haynes, Karl Kuchler. *PLoS Pathogens* 10: e1004211. DOI: 10.1371/journal.ppat.1004211

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