Healthcare industry BW

Focus on new antimycotics targets

Yeast infections are becoming a growing threat in intensive care medicine and only a small number of effective drugs – so-called antimycotics – are available. The scientist Dr. Steffen Rupp from Stuttgart is investigating the individual steps of the infection process in order to find key mechanisms in the fungus that can be targeted.

Dr. Steffen Rupp is head of the Department of Molecular Biotechnology at the Fraunhofer Institute for Interfacial Engineering and Biotechnology (IGB) in Stuttgart

The fungus Candida albicans is found in small quantities on the skin and mucosa of the nose and throat areas of humans; the fungus is also a natural component of the microbial flora of the

gastrointestinal tract. Candida albicans leads an inconspicuous life as long as the human immune system and local defence mechanisms remain intact. Disease symptoms only appear when the finely regulated balance is disturbed by a serious disease or the consumption of certain drugs.

While local, superficial infections such as oral thrush can be irritating, Candida infections may have more serious consequences in people who are undergoing chemotherapy, for example, where they can lead to systemic infections (candidiasis). In the case of systemic infections, the fungus enters lower tissue sections and spreads throughout the entire body via the blood. "One of the major ports into the human body is the colon," said Dr. Steffen Rupp from the Stuttgart-based Fraunhofer Institute for Interfacial Engineering and Biotechnology (IGB). "Candida infections in the colon very rapidly cause damage to the intestinal mucus." In intensive care medicine, Candida spp. have become the fourth most frequent cause of sepsis, and the number of incidences is increasing.

Understanding the molecular mechanisms

However, there are only a handful of therapeutic options for the effective treatment of Candida infections. "Until now, only a small number of drugs have been available, and the fungi are becoming more and more resistant to the substances used," said Rupp. Systemic Candida albicans infections are still associated with a mortality rate of up to 40 per cent. Therefore, the search for new drugs – so-called antimycotics – is an intrinsic goal of research. "However, in order to be able to identify potential targets for new pharmaceutical substances, we need to understand the molecular mechanisms of the infection process," said Rupp, who heads up the Department of Molecular Biotechnology.

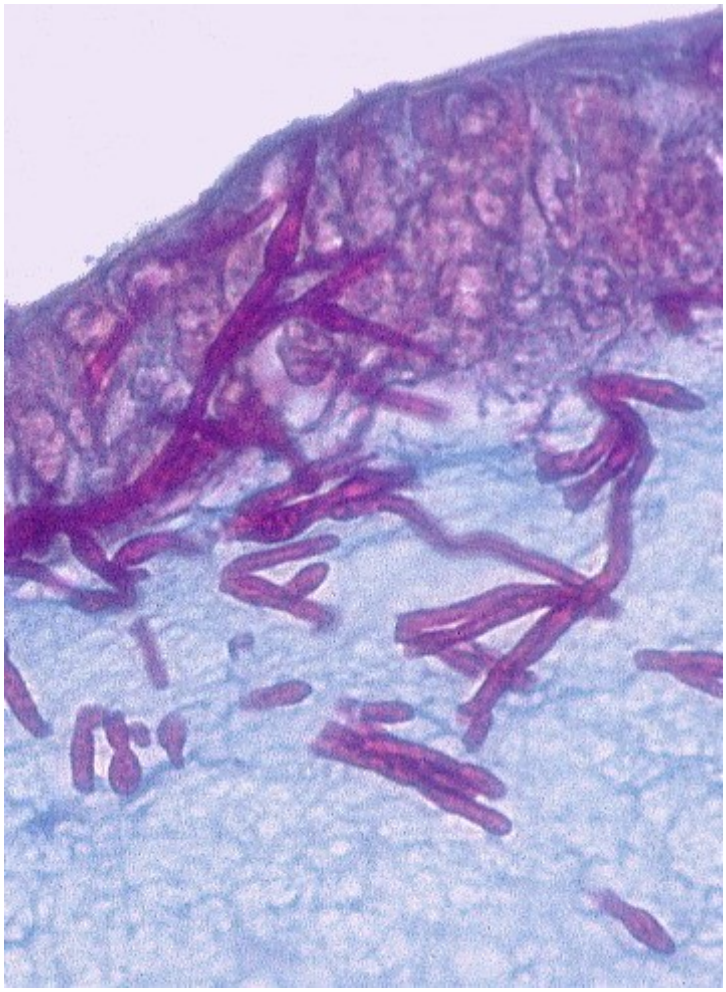
Rupp and his team mainly focus on the fungal cell wall. In contrast to human cells, fungal cells are surrounded by a cell wall of high mechanical stability. This complex structure of sugar polymers not only protects the fungus, but is also the first point of contact with human tissue when infection occurs. Candida albicans' ability to successfully attach to the host cells is due to the fact that their cell wall is equipped with certain proteins, known as adhesins, which attach directly to human cells.

Blockage prevents colonisation

Candida genes carry the information for more than 100 different cell surface proteins which all have a specific function during the fungus' adhesion to cells or tissue. "The expression of certain surface proteins during the process of infection depends on the particular tissue surface colonised by the fungus," said Rupp. If it were possible to specifically block these adhesins, the colonisation of Candida could be averted, thus preventing the development of a life-threatening infection.

Rupp and his team have developed various methods to identify the adhesins and the proteins that cause the fungus to invade the tissue. One method involves comparing the protein patterns of harmless yeast strains with those obtained from patient samples. The researchers identified numerous proteins that only occur in pathogenic strains, and which might "in some way be responsible for the infection", said Rupp.

Another method involves the introduction of specific mutations in certain Candida genes in order to either switch off or overexpress the genes. Rupp uses specific tissue models to simulate the surface of human tissues, including the intestinal mucosa, as realistically as possible, in order to investigate the effects of mutations on the virulence of the fungus. "Candida isolates from patients have been shown to take just two to three days to penetrate and destroy these tissue equivalents", said the researcher adding that "these isolates were full of fungal cells." Some mutants have lost the ability to grow into the tissue. The researchers believe that this particular gene encodes a factor that is of key



Clinical Candida albicans isolate penetrates a colon mucosa model, consisting of human intestinal cells (enterocytes, Caco-2) grown on a collagen matrix, just 18 hours after incubation (incubation at 37°C).

importance for the fungus' ability to invade tissue. This finding could lead to numerous therapeutic options.

Assay to test efficacy and toxicity

In collaboration with EMC microcollections GmbH based in Tübingen, Rupp is using the latest findings to screen for antimycotic substances. Classical procedures focus on assessing the direct effect of a substance library on the fungus. “This mainly helps to assess whether the fungus is growing or not,” said Rupp. A new approach now puts the screening in the context of the host organism. “We create a small infection unit in which we bring living human cells and Candida albicans cells into contact with each other in the test tube,” said the researcher. The fungus immediately develops its pathogenic potential and expresses the exact proteins that are required for invasive growth and that are being targeted by the test substances under investigation. This method also has the advantage of enabling the compatibility of the substances with human tissue to be tested in the same experiment. This provides the researchers with immediate information as to which substances have a realistic chance of becoming an antimycotic drug in the future. “We are able to immediately exclude all toxic compounds,” said Rupp.

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Fungi – an introduction