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S6.5b  Genomics and metagenomics of Madurella mycetomatis

Madurella mycetomatis is the most frequently identified causative agent of mycetoma cases. However, 10% of grains also contained bacterial reads suggestive of secondary infections. A thorough understanding of the genetic structure and diversity of fungi causing mycetoma is essential for the development of new diagnostic methods and for identifying potential drug targets.

Shotgun metagenomic analysis of DNA from mycetoma grains confirmed that M. mycetomatis was the predominant causative agent of mycetoma Sudan; however, 10% of grains also contained bacterial reads suggestive of secondary infections. A thorough understanding of the genetic structure and diversity of fungi causing mycetoma is essential for the development of new diagnostic methods and for identifying potential drug targets.

S6.5c  MycoDOS: identifying drugs which can penetrate the mycetoma grain

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Mycetoma is a neglected tropical disease characterized by large subcutaneous swellings and the formation of grains. Madurella mycetomatis is the most common causative agent. Currently, mycetoma is treated with a combination of itraconazole...
therapy and surgery with lower success rates, resulting often in aspiration and social stigma. To improve the current therapeutic outcomes, a novel drug is needed. Due to the lack of interest in the pharmaceutical industry, in-vivo or in-vitro drug discovery programs for mycosis were established called MycoDS.

In total, 1560 compounds were screened for in vitro activity against M. yeastitum and many more are currently being screened. Compounds that were able to inhibit growth at 100 μg, 25 μg, and had an IC50 < 8 μg were selected for studying the in vivo efficacy in an M. yeastitum animal model in the intermound Gabala subfuselli. One of the 1560 compounds screened against M. yeastitum, 352/ was able to induce growth at 100 μg and 23 of those most active were screened in vivo. Out these 23, rates did not change between 100 μg and 23 of those most active were screened in vivo. None of these 37 assays tested, olefinim, fenbendazole, MMV013583, MMV012247, MMV477068, and MMV718237. Based on these results, 6 compound series were selected for further evaluation, 3 series included (series 1), the aminoimidazoles (series 5), the phenothiazine (series 2), the phenoxathine (series 3), and the hydroxybenzidine inhibitors (series 4). The mechanism of 1 was tested in vivo. These 37 compounds were screened. By analyzing the in vitro activity and in vivo efficacy in relation to the chemical properties of the molecules, it appears that the LogD value of a compound was important for penetrating into the mycosis grain.

In conclusion, using an in-vivo drug discovery approach for mycosis we were able to identify novel lead compounds. Some of these compounds were highly active against M. yeastitum (stilbene, amonitriene, phenoxyacetone, and kerosene), while other compounds such as the benzimidazoles also were active against other causative agents as well. Screening more analogs of identified compounds allowed us also to identify chemical properties which are favorable for grain penetration in vivo. This will allow us to chemically design more active compounds for this difficult to treat infection.

S6td
Molecular identification of mycosis causative agents from patients in hospital setting in Senegal

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S7Id
Reliability ofbedside point-of-care tests for Candida neoformans, M. tuberculosis and S. pneumoniae in adults living with HIV presenting with suspected central nervous system infection (CNS) in low- and middle-income settings: Preliminary results from the DREAMM study

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S7d
Divergent EGFR/MAPK-mediated immune responses to clinical Candida pathogens in vulvovaginal candidiasis

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3More than just clinical symptoms: clinical diagnosis, treatment and pathogenesis of deep-seated candidiasis, September 23, 2022, 10:30 AM - 12:00 PM

Objectives: Vulvovaginal candidiasis (VVC) is characterized by symptomatic inflammatory responses in the vagina caused by Candida albicans and non-albicans Candida (NAC) species. The epidemiological growth factor receptor (EGFR): mitogen-activated protein kinase (MAPK) signaling pathway has been linked to immune responses of oral epithelial cells in C. albicans exposure, but whether this pathway plays a similar response in vaginal epithelial cells is not determined.

Methods: The activation of EGFR and MAPK signaling pathways in vaginal epithelial cells infected with C. albicans was determined by RNA sequencing and Western blot. The relationship between EGFR and MAPK signaling was verified via inhibition of EGFR and construction of EGFR overexpressing cells. Enzyme-linked immunosorbent assay (ELISA) and Real Time Cellular Analysis (RTCA) techniques were used to detect the effect of EGFR-MAPK signaling pathway on regulating the secretion of inflammatory cytokines and cell damage induced by C. albicans. The results of VVC model infected by C. albicans was constructed, and the role of EGFR signaling pathway in regulating fungal burden, vaginal inflammation, and epithelial damage was determined by Periodic Acid–Schiff stain and immunofluorescence.

Results: We observed that phosphorylation of EGFR and p38 was continuously activated in vaginal epithelial cells by C. albicans strain SC5314. The response is not in a biphasic manner that is critical for oral epithelial cells to discriminate the morphology of C. albicans. When compared with SC5314, a highly zymo-resistant C. albicans isolate 1052 can induce a stronger phosphorylated signal of EGFR and p38, while clinically-resident NAC strains including C. tropicalis, C. glabrata, C. parapsilosis, and C. auris trangos higher levels of phosphorylated ERK1/2 and a Fox-3 than C. albicans. Consistently, inhibition of EGFR significantly reduced inflammatory response and epithelial damage induced by C. albicans in vitro and in vivo, while inhibition of p38 led to great loss of epithelial damage triggered by both C. albicans and NAC species.

Conclusion: These results confirm the importance of the EGFR-MAPK signaling in VVC pathogenesis and highlight the remarkable immunologic differences between C. albicans and NAC species in host-microbe interactions.