Nature Reviews Microbiology | AOP, published online 3 September 2012; doi:10.1038/nrmicro2881

BRAND X

> “inhibitors of EGFR and HER2 reduced *C. albicans* endocytosis.”

Although *Candida albicans* is part of the normal human flora on mucosal surfaces, under certain circumstances it can overgrow, causing conditions such as oropharyngeal candidiasis (OPC). Here, Filler and colleagues show that a key step in this process, epithelial cell invasion, can be mediated by interaction with epidermal growth factor receptor (EGFR) and HER2 (also known as ERBB2) on epithelial cells.

C. albicans is known to invade epithelial cells either actively, using invasive hyphae, or through host cell-mediated endocytosis. The latter method involves interaction with E-cadherin on epithelial cells, but other factors may also be involved. Indeed, using affinity purification assays, Filler and colleagues found that fungal hyphae interact with EGFR and its heterodimer binding partner, HER2. Further analysis showed that the two receptors interact with two *C. albicans* invasins, Als3 and Ssa1, as hyphae from fungi lacking these proteins did not bind to EGFR and HER2, and complementation of the mutants with wild-type invasins restored the interaction.

Activation of EGFR and HER2 results in their tyrosine autophosphorylation and triggering of downstream signalling pathways. Consistent with this, *C. albicans* hyphae induced phosphorylation of the two receptors within 10 minutes of infection, and hyphae from invasin-deficient fungi induced less EGFR and HER2 phosphorylation than wild-type hyphae. Furthermore, inhibitors of EGFR and HER2 reduced *C. albicans* endocytosis. Interestingly, EGFR alone was not sufficient to induce endocytosis of *C. albicans* (for example, when expressed in fibroblasts), which indicates that EGFR and HER2 function cooperatively.

Finally, the authors assessed the relevance of their findings using a mouse model of OPC. They observed that oral infection with *C. albicans* triggered phosphorylation of EGFR and HER2 and that this could be reduced using a dual EGFR and HER2 inhibitor. Importantly, treatment with the inhibitor significantly reduced oral fungal burden.

Thus, *C. albicans* triggers its endocytosis by binding to EGFR–HER2 as well as E-cadherin on epithelial cells. Interestingly, *Listeria monocytogenes* also interacts with a tyrosine kinase receptor and E-cadherin to induce its endocytosis, so this might be a common pathway used by pathogens to invade host cells.

Rachel David

ORIGINAL RESEARCH PAPER Zhu, W. *et al.* EGFR and HER2 receptor kinase signaling mediate epithelial cell invasion by *Candida albicans* during oropharyngeal infection. *Proc. Natl Acad. Sci. USA* 12 Aug 2012 (doi:10.1073/pnas.1117676109)