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MICROBIOLOGY IN SCHOOLS ADVISORY COMMITTEE
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Candida: a fungus of the healthy human microbiome – but one that can bite the hand that feeds it

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The teaching of biology has rightly emphasised the emergence of 'deadly viruses', 'rare bacterial infections' and 'exotic parasites' but has not reflected the importance of fungi as common disease causing organisms. We know fungi as the cause of skin and nail infections and as the agents of human dandruff but it is less well known that, collectively, fungi also kill as many people as HIV, TB, and more people than malaria, breast or prostate cancer (Brown *et al.*, 2012). Deadly fungal infections normally do not occur in healthy individuals but they can cause life-threatening systemic infections in people with damaged immune systems, such as patients undergoing cancer and intensive care treatment or surgery and in people infected with other diseases such as HIV/ AIDS.

One of the major clinically relevant fungal species is *Candida*; a common yeast-like fungus that is responsible for thrush infections of the mucous membranes and invasive systemic disease that can damage all the major essential organs of the body. About a dozen species of *Candida* cause disease of which *Candida albicans* is the most prevalent species in terms of incidence and mortality. Paradoxically this microbe is carried harmlessly in the microbiome in as much as 50% of the human population with no ill effects. However, when normal defences are severely impaired, disease can result and may in certain circumstances be life threatening. *Candida* species collectively are the fourth most common cause of bloodstream infections in hospitals in the US (Kullberg & Arendrup, 2016). A very worrying newly emerging species called *Candida auris* has emerged where many strains are highly resistant to the major antifungal drugs that are used to treat fungal infections (Spivak & Hanson, 2018).

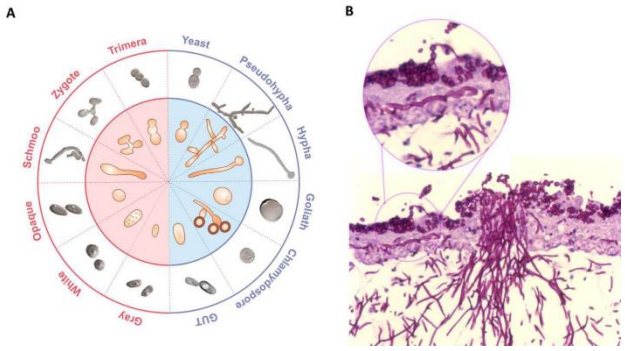

Figure 1. A. The various cell forms of *C. albicans*. Red forms are concerned with creating genetic variability, blue forms are those involved in infections. **B**. Invasion of epithelial surfaces by yeasts cells forming hyphae that breach the tissue surface (Gow & Yadav, 2017).

One of the factors contributing to the diseases caused by *C. albicans* is its ability to change shape and live in multiple forms (**Figure 1**). Budding yeast cells are able to disseminate in the human body, and filamentous forms (hyphae, pseudohyphae) are adapted to penetrate tissues and invade human tissues (Gow *et al.*, 2011) (**Figure 2**). It is a fungus that does not seem to undergo meiosis, nonetheless it is able to create tremendous genetic variability and to mutate and adapt to become drug resistant. Its ability to switch between different morphologies and to undergo these genetic changes means it is a

moving target for both the immune system and antibiotic treatment, making it difficult for our natural defences and for doctors to get on top of infections.

The cell wall of the fungus gives it its characteristic shape and is constructed from molecules that are not found in humans or animals. The human immune system is trained to recognise these specific molecules in the wall to identify the presence of an invading fungus (Erwig & Gow, 2016). Drugs that damage the fungal wall are excellent antifungal agents since they do not affect human cells. But, the fungal cell wall is a dynamic structure that is capable of changing its composition and rebuilding itself when it is damaged by antifungal antibiotics or digestive enzymes and oxidising agents presented by human white blood cells (Brown *et al.*, 2014; Erwig & Gow, 2016).

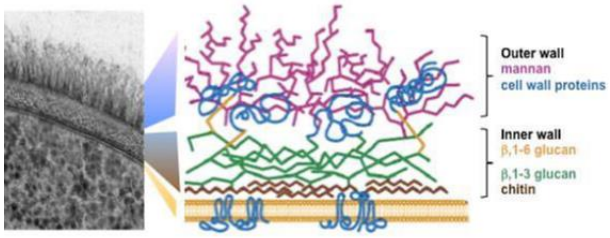

Figure 2. *C. albicans* cell wall structure. The fungal cell wall is composed of two layers. The inner layer of chitin and glucans gives the wall mechanical strength and is the target of antifungal antibiotics such as echinocandins. The outer layer of a mannose based fibres protects the vulnerable inner cell wall layer from attack by enzymes. All of the components of the wall are recognised by specific receptors in cells of the immune system (Gow et al., 2011.)

Many antibiotics used to treat bacterial infections (penicillin, vancomycin and others) attack the cell wall. Similarly, echinocandins are natural antibiotics and are used in hospitals to treat fungal infections. These drugs work by preventing cell wall β-(1,3) glucan synthesis (Walker *et al.*, 2013). But the fungus can adapt. Mutations in the gene that encodes the enzyme that is inhibited by these drugs can make the fungus resistant (Barnes *et al.*, 2015). Alternatively, the fungus can make more chitin in the cell wall to compensate for the lack of β-glucan. This makes the cell wall thicker, stronger and less susceptible to echinocandins (Walker *et al.*, 2013). Understanding how the cell wall assembles and which proteins are involved in its remodelling will contribute to design of new targets for new antifungal drugs.

Azoles are a second class of compound used to treat *Candida* infections. These drugs block fungal sterol biosynthesis. But, *Candida* species can quickly duplicate chromosomes that encode genes that result in azole resistance, and there are problems due to the accumulation of mutations conferring drug resistance and the fungus's ability to spit out antifungal drugs *via* specialist drug efflux pumps (Fairlamb *et al.*, 2016).

At present there are no vaccines against any fungus (Gow & Netea, 2016), but it is possible that novel antibody-based drugs will be designed that complement the use of antibiotics in helping us to overcome or prevent serious fungal infections. Further studies into the biology of these underappreciated culprits of human disease could, in the future, prevent the deaths of millions and improve the quality of life of vulnerable patients with damaged immune systems.

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