

The role of the fungal cell wall in antifungal drug susceptibility and immune recognition: opportunities for new antifungal immunotherapies

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The fungal cell wall is a dynamic polysaccharide-rich organelle which maintains cellular integrity. The polysaccharides, chitin and β -1,3-glucan, give the wall its mechanical strength and an outer fibrillar layer of highly glycosylated mannoproteins include important virulence factors such as adhesins. Embedded in the wall are carbohydrate active enzymes that act upon cell wall polysaccharides and generate cross links. Fungi can alter the composition, structure and properties of their walls in response to different internal and external stimuli such as exposure to antifungal drugs.

We have investigated how the cell wall structure, composition and proteomes of drug sensitive and drug resistant clinical isolates of *Candida* species is altered in response to echinocandin drugs. These alterations influence host interactions, immune recognition and antifungal drug tolerance and resistance.

Our analysis of the response of pathogenic fungi to antifungal drug pressure has highlighted changes in cell wall composition such as elevated chitin levels and the increased expression of cell surface proteins. This has allowed us to select novel, conserved cell surface protein that are involved in cell wall remodelling, such as chitin-glucan cross-linking enzymes, as targets for immunotherapy. We have developed monoclonal antibodies against these specific cell surface epitopes and spun out a company Brigid bio from the University of Aberdeen. These antibodies bind *C. albicans* with stronger binding to hyphae and recognise drug resistant isolates of *Candida auris*, *Candida glabrata*, *Candida tropicalis* and *Candida parapsilosis*. They enhance phagocytosis by macrophages and are protective in mouse models of systemic candidiasis. We are developing the monoclonal antibodies as a new generation of biologics-based antifungal immunotherapies against drug resistant infections.