The Dark Side of the Wall: Atomic Force Microscopy Revelations on Drug Resistance and Adhesion

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Hélène Martin-Yken[1], Cécile Formosa-Dague[1], Marion Schiavone[1], and Etienne Dague[2].

[1] *LISBP, INSA, Université de Toulouse, INRA UMR792, CNRS UMR5504, 135 avenue de Rangueil, Toulouse, F-31077, France*
[2] *LAAS, CNRS, 7 Avenue du Colonel Roche, Toulouse, F-31077, France*

e-mail: helene.martin@insa-toulouse.fr

The cell wall of yeast and fungi plays a crucial role in the way these cells sense, respond and adapt to environmental perturbations. Using recent Atomic Force Microscopy technological developments, the biophysical consequences of different stresses on the major human fungal pathogen, *Candida albicans,* were imaged and measured. Morphological changes were characterized at the nanoscale, including surface roughness, elasticity and adhesive properties. Exposure to the antifungal Caspofungin was shown to cause a deep cell wall remodeling with major modifications of chitin and beta-glucan content. Remarkably, a low dose of Caspofungin (*i.e.*, 0.5 × MIC) provoked a strong expression of adhesive proteins on the cell surface of *C. albicans,* a side effect highly relevant considering its wide spread medical use. Moreover, Single Molecule Force Spectroscopy (SMFS) experiments by AFM allowed us to visualize the organization of these adhesins, to map them on the cell surface and to quantify the adhesion forces, including on cells undergoing mophogenetic differentiation. Combined with molecular biology tools, this approach enabled us to unravel the particular contribution of previously uncharacterized proteins (PGA22 and PGA59) to *C. albicans* adhesion mechanism. In addition, functionalizing the AFM tip with antibodies allows following the appearance of specific proteins, while precisely mapping them at the cell surface and even measuring the time scale of their progression through the cell wall. The example of Hwp1 appearance on geminating hyphal tubes will be illustrated.