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Commentary

Fungal Biofilm Resilience in Medical Device-Associated Infections

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DESCRIPTION

Fungal biofilms represent a formidable challenge in clinical settings, especially in infections related to medical devices such as catheters, prosthetic valves, and orthopedic implants. *Candida* species, particularly *Candida albicans*, are the primary culprits in fungal biofilm-related infections. Their ability to form structured biofilms on abiotic surfaces confers resistance to antifungal therapies and host immune defenses. It provides an in-depth overview of the molecular mechanisms underlying fungal biofilm resilience, including gene expression profiles that regulate adhesion, Extracellular Matrix (ECM) formation, drug resistance, and metabolic adaptation. The clinical implications of these mechanisms in the management of device-associated infections are also discussed, along with current strategies and emerging approaches for prevention and eradication.

Medical Device-Associated Infections (MDAIs) caused by fungal pathogens have become increasingly prevalent, particularly in immunocompromised and critically ill patients. Fungal biofilms are structured microbial communities that adhere to both biotic and abiotic surfaces and are embedded in a self-produced extracellular matrix. The biofilm lifestyle allows fungal cells to withstand antifungal treatment and host immune responses, making these infections recalcitrant and often chronic. Among fungal pathogens, *Candida albicans* is the most studied, but non-albicans species such as *Candida glabrata*, *Candida tropicalis*, and *Candida parapsilosis* are also frequently implicated.

Fungal biofilm formation is a multistep process that involves initial adhesion, proliferation, ECM production, maturation, and dispersion. The early phase begins with yeast cells adhering to the surface of medical devices. Key adhesins such as *ALS1*, *ALS3*, and hyphal wall protein 1(*HWP1*) are upregulated during this phase, mediating attachment and initiating morphogenic transformation into hyphal forms. The hyphal transition is critical for biofilm maturation and is regulated by the *EFG1*, *CPH1*, and *TEC1* transcription factors.

The mature biofilm consists of a dense network of yeast, hyphal, and pseudohyphal cells encased in an ECM rich in β-glucans, proteins, lipids, and extracellular DNA (eDNA). The matrix not only provides structural integrity but also acts as a physical barrier to antifungal agents. Genes such as *FKS1* (β-1,3-glucan synthase) and *ZAP1* are instrumental in ECM synthesis and regulation.

Fungal biofilms exhibit a distinct gene expression profile compared to planktonic cells. These changes contribute to biofilm resilience. Adhesin genes such as *ALS3*, *HWP1*, and *EPA1* (in C. glabrata) are highly upregulated during early biofilm development. The *EFG1–CPH1* pathway governs morphogenesis and biofilm maturation, promoting the yeast-to-hyphae transition essential for three-dimensional biofilm architecture. The gene *ZAP1* regulates ECM composition by controlling zinc homeostasis and repressing matrix production. *RLM1*, a transcription factor in the cell wall integrity pathway, regulates genes like *FKS1* and *CHS2*, contributing to cell wall remodeling and β-glucan deposition in the matrix. One of the most clinically relevant aspects of fungal biofilm resilience is their reduced susceptibility to antifungal agents.

Fungal biofilms on medical devices pose significant diagnostic and therapeutic challenges. They are often resistant to first-line antifungals, necessitating device removal and systemic therapy. For instance, central venous catheter infections by *C. albicans* may require catheter extraction and treatment with echinocandins or amphotericin B. However, even these agents show reduced efficacy against mature biofilms. Biofilm-associated infections are also more likely to recur due to the persistence of biofilm "persister" cells-quiescent subpopulations that tolerate high drug concentrations. These cells can reseed infection after treatment discontinuation, underscoring the need for strategies that specifically target biofilm structures and survival pathways.

ALT involves instilling high concentrations of antifungals into the lumen of infected catheters. Although effective in early-stage biofilms, ALT has limited success against mature biofilms due to matrix penetration barriers and efflux mechanisms. Emerging antifungals such as ibrexafungerp and rezafungin show promise against biofilm-forming fungi. Combination therapies (e.g., fluconazole with echinocandins) may also overcome resistance by targeting multiple pathways simultaneously. Development of antifungal coatings (e.g., silver nanoparticles, chlorhexidine, and antimicrobial peptides) on medical devices can prevent initial

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fungal adhesion. Surface modifications that reduce protein adsorption and microtopographic designs that prevent cell clustering are under active investigation. CRISPR-Cas9-based gene editing has enabled precise manipulation of biofilm-associated genes. Targeting genes like *ZAP1*, *ALS3*, or *FKS1* could yield novel antifungal strategies that disarm biofilm resilience at its molecular core.

CONCLUSION

Fungal biofilms are a key factor in the persistence and recurrence of medical device–associated infections. Their resilience is driven by complex gene regulatory networks that govern adhesion, matrix production, antifungal resistance, and metabolic adaptation. Current treatment options remain limited, often requiring invasive interventions and combination therapies. Advances in molecular understanding of biofilm biology-particularly gene expression dynamics-will prepare for more effective preventive and therapeutic measures in combating these recalcitrant infections.