A Metabolic Switch to Virulence: How Fungal Sterols Shape Host Immunity and Disease Outcome

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Fungal infections caused by members of the Fusarium oxysporum species complex are an emerging clinical challenge, often associated with high mortality and limited treatment options. Despite their increasing medical importance, the microbial traits that drive pathogenicity in mammalian hosts remain poorly defined. In this study, we identify remodeling of sterol metabolism as a key feature distinguishing clinically derived isolates. These strains exhibit elevated production and extracellular release of ergosterol, a major fungal membrane lipid. Functionally, this metabolic shift has profound effects on host immunity. Increased sterol availability promotes inflammasome activation and caspase-1–dependent pyroptotic cell death in macrophages. At the same time, it selectively suppresses chemokine production through IL-10 and TGF-β–associated pathways, resulting in impaired recruitment of immune cells despite robust pro-inflammatory cytokine induction. This uncoupling of cytokine production from immune cell recruitment creates a paradoxical inflammatory state that favors fungal persistence and dissemination in vivo. Importantly, these findings reveal that ergosterol is not merely a structural membrane component or antifungal target, but also acts as an immunomodulatory molecule that reshapes host–pathogen interactions. More broadly, our work highlights how quantitative changes in core metabolic pathways can drive virulence by reprogramming host immunity, providing a new framework for understanding fungal pathogenicity and identifying potential therapeutic vulnerabilities