PLB-985 Neutrophil-Like Cells as a Model To Study Aspergillus fumigatus Pathogenesis.

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Projects

Communication via extracellular vesicles between immune cells and the human-pathogenic fungus *Aspergillus fumigatus*
Details

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Molecular Mechanisms of lipid raft formation
Details

Abstract

Fungal infections remain a major global concern. Emerging fungal pathogens and increasing rates of resistance mean that additional research efforts and resources must be allocated to advancing our understanding of fungal pathogenesis and developing new therapeutic interventions. Neutrophilic granulocytes are a major cell type involved in protection against the important fungal pathogen Aspergillus fumigatus, where they employ numerous defense mechanisms, including production of antimicrobial extracellular vesicles. A major drawback to work with neutrophils is the lack of a suitable cell line system for the study of fungal pathogenesis. To address this problem, we assessed the feasibility of using differentiated PLB-985 neutrophil-like cells as an in vitro model to study A. fumigatus infection. We find that dimethylformamide-differentiated PLB-985 cells provide a useful recapitulation of many aspects of A. fumigatus interactions with primary human polymorphonuclear leukocytes. We show that differentiated PLB-985 cells phagocytose fungal conidia and acidify conidia-containing phagolysosomes similar to primary neutrophils, release neutrophil extracellular traps, and also produce antifungal extracellular vesicles in response to infection. In addition, we provide an improved method for the isolation of extracellular vesicles produced during infection by employing a size exclusion chromatography-based approach. Advanced liquid chromatography-tandem mass spectrometry (LC-MS/MS) proteomics revealed an enrichment of extracellular vesicle marker proteins and a decrease of cytoplasmic proteins in extracellular vesicles isolated using this improved method. Ultimately, we find that differentiated PLB-985 cells can serve as a genetically tractable model to study many aspects of A. fumigatus pathogenesis.

IMPORTANCE Polymorphonuclear leukocytes are an important defense against human fungal pathogens, yet our model systems to study this group of cells remain very limited in scope. In this study, we established that differentiated PLB-985 cells can serve as a model to recapitulate several important aspects of human polymorphonuclear leukocyte interactions with the important human fungal pathogen Aspergillus fumigatus. The proposed addition of a cultured neutrophil-like cell line to the experimental toolbox to study fungal pathogenesis will allow for a more mechanistic description of neutrophil antifungal biology. In addition, the easier handling of the cell line compared to primary human neutrophils allowed us to use PLB-985 cells to provide an improved method for isolation of neutrophil-derived extracellular vesicles using size exclusion chromatography. Together, these results provide significant tools and a baseline knowledge for the future study of neutrophil-derived extracellular vesicles in the laboratory.

Identifier

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