Human Neutrophils Produce Antifungal Extracellular Vesicles against Aspergillus fumigatus.

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Abstract

Polymorphonuclear granulocytes (PMNs) are indispensable for controlling life-threatening fungal infections. In addition to various effector mechanisms, PMNs also produce extracellular vesicles (EVs). Their contribution to antifungal defense has remained unexplored. We reveal that the clinically important human-pathogenic fungus Aspergillus fumigatus triggers PMNs to release a distinct set of antifungal EVs (afEVs). Proteome analyses indicated that afEVs are enriched in antimicrobial proteins. The cargo and the release kinetics of EVs are modulated by the fungal strain confronted. Tracking of afEVs indicated that they associated with fungal cells and even entered fungal hyphae, resulting in alterations in the morphology of the fungal cell wall and dose-dependent antifungal effects. To assess as a proof of concept whether the antimicrobial proteins found in afEVs might contribute to growth inhibition of hyphae when present in the fungal cytoplasm, two human proteins enriched in afEVs, cathepsin G and azurocidin, were heterologously expressed in fungal hyphae. This led to reduced fungal growth relative to that of a control strain producing the human retinol binding protein 7. In conclusion, extracellular vesicles produced by neutrophils in response to A. fumigatus infection are able to associate with the fungus, limit growth, and elicit cell damage by delivering antifungal cargo. This finding offers an intriguing, previously overlooked mechanism of antifungal defense against A. fumigatus IMPORTANCE Invasive fungal infections caused by the mold Aspergillus fumigatus are a growing concern in the clinic due to the increasing use of immunosuppressive therapies and increasing antifungal drug resistance. These infections result in high rates of mortality, as treatment and diagnostic options remain limited. In healthy individuals, neutrophilic granulocytes are critical for elimination of A. fumigatus from the host; however, the exact extracellular mechanism of neutrophil-mediated antifungal activity remains unresolved. Here, we present a mode of antifungal defense employed by human neutrophils against A. fumigatus not previously described. We found that extracellular vesicles produced by neutrophils in response to A. fumigatus infection are able to associate with the fungus, limit growth, and elicit cell damage by delivering antifungal cargo. In the end, antifungal extracellular vesicle biology provides a significant step forward in our understanding of A.

fumigatus host pathogenesis and opens up novel diagnostic and therapeutic possibilities.

Identifier

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