Hypoxia-inducible factor 1α modulates metabolic activity and cytokine release in anti-Aspergillus fumigatus immune responses initiated by human dendritic cells.

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Details

Abstract

The mold Aspergillus fumigatus causes life-threatening infections in immunocompromised patients. Over the past decade, new findings in research have improved our understanding of A. fumigatus-host interactions, including the recent identification of myeloid-expressed hypoxia-inducible factor 1α (HIF-1α) as a relevant immune-modulating transcription factor and potential therapeutic target in anti-fungal defense. However, the function of HIF-1α signaling for human anti-A. fumigatus immunity is still poorly understood, including its role in dendritic cells (DCs), which are important regulators of anti-fungal immunity. This study investigated the functional relevance of HIF-1α in the anti-A. fumigatus immune response initiated by human DCs. Hypoxic cell culture conditions were included because hypoxic microenvironments occur during A. fumigatus infections and may influence the host immune response. HIF-1α was stabilized in DCs following stimulation with A. fumigatus under normoxic and hypoxic conditions. This stabilization was partially dependent on dectin-1, the major receptor for A. fumigatus on human DCs. Using siRNA-based

HIF-1α silencing combined with genome-wide transcriptional analysis, a modulatory effect of HIF-1α on the anti-fungal immune response of human DCs was identified. Specifically, the difference in the transcriptomes of HIF-1α silenced and non-silenced DCs indicated that HIF-1α contributes to DC metabolism and cytokine release in response to A. fumigatus under normoxic as well as hypoxic conditions. This was confirmed by further down-stream analyses that included metabolite analysis and cytokine profiling of a time-course infection experiment. Thereby, this study revealed a so far undescribed functional relevance of HIF-1α in human DC responses against A. fumigatus.

Involved units

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