Identification of immunogenic antigens from *Aspergillus fumigatus* by direct multi-parameter characterization of specific conventional and regulatory CD4+ T cells.

Bacher P, Kniemeyer O, Teutschbein T, Thoen M, Vödisch M, Wartenberg D, Scharf DH, Koester-Eiserfunke N, Schütte M, Dübel S, Assenmacher M, Brakhage AA, Scheffold A (2014) Identification of immunogenic antigens from *Aspergillus fumigatus* by direct multi-parameter characterization of specific conventional and regulatory CD4+ T cells. *Journal of Immunology* 197(7), 3332-3343.

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Abstract

CD4(+) T cells orchestrate immune responses against fungi, such as *Aspergillus fumigatus*, a major fungal pathogen in humans. The complexity of the fungal genome and lifestyle questions the existence of one or a few immune-dominant Ags and complicates systematic screening for immunogenic Ags useful for immunotherapy or diagnostics. In this study, we used a recently developed flow cytometric assay for the direct ex vivo characterization of A. fumigatus-specific CD4(+) T cells for rapid identification of physiological T cell targets in healthy donors. We show that the T cell response is primarily directed against metabolically active *A. fumigatus* morphotypes and is stronger against membrane protein fractions compared with cell wall or cytosolic proteins. Further analysis of 15 selected single *A. fumigatus* proteins revealed a highly diverse reactivity pattern that was donor and protein dependent. Importantly, the parallel

assessment of T cell frequency, phenotype, and function allowed us to differentiate between proteins that elicit strong memory T cell responses in vivo versus Ags that induce T cell exhaustion or no reactivity in vivo. The regulatory T cell (Treg) response mirrors the conventional T cell response in terms of numbers and target specificity. Thus, our data reveal that the fungal T cell immunome is complex, but the ex vivo characterization of reactive T cells allows us to classify Ags and to predict potential immunogenic targets. A. fumigatus-specific conventional T cell responses are counterbalanced by a strong Treg response, suggesting that Treg-depletion strategies may be helpful in improving antifungal immunity.

Involved units

Molecular and Applied Microbiology Axel Brakhage Read more

Leibniz-HKI-Authors



Axel A. Brakhage

Details



Olaf Kniemeyer

Details



Nora Köster-Eiserfunke

Details



Daniel H. Scharf

Details



Janka Teutschbein

Details



Martin Vödisch

Details



Dirk Wartenberg

Details

Identifier

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