

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

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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.

Beteiligte Forschungseinheiten

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