# β-1,3-glucan-lacking *Aspergillus fumigatus* mediates an efficient antifungal immune response by activating complement and dendritic cells.

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## Abstract

Complement system and dendritic cells (DCs) form - beside neutrophils and macrophages - the first line of defense to combat fungal infections. Therefore, we here studied interactions of these first immune elements with *Aspergillus fumigatus* lacking ß-1,3-glucans (fks1tetOnrep under repressed conditions) to mechanistically explain the mode of action of echinocandins in more detail. Echinocandins are cell wall active agents blocking β-glucan synthase, making the *A. fumigatus* fks1tetOn mutant a good model to study immune-modulatory actions of these drugs. We now demonstrate herein, that complement was activated to significantly higher levels by the fks1-deficient strain compared to its respective wild type. This enhanced covalent linking of

complement fragments to the *A. fumigatus* fks1tetOnrep mutant further resulted in enhanced DC binding and internalization of the fungus. Additionally, we found that fks1tetOnrep induced a Th1-/Th17-polarizing cytokine profile program in DCs. The effect was essentially dependent on massive galactomannan shedding, since blocking of DC-SIGN significantly reduced the fks1tetOnrep-mediated induction of an inflammatory cytokine profile. Our data demonstrate that lack of ß-1,3-glucan, also found under echinocandin therapy, results in improved recognition of *Aspergillus fumigatus* by complement and DCs and therefore not only directly affects the fungus by its fungistatic actions, but also is likely to exert indirect antifungal mechanisms by strengthening innate host immune mechanisms. Abbreviations: C: complement; CR:complement receptor; DC: dendritic cell; iDC: immature dendritic cell; DC-SIGN: Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin; ERK: extracellular signal-regulated kinases; JNK : c-Jun N-terminal kinases; MAPK: mitogen-activated protein kinase; NHS: normal human serum; PRR: pattern recognition receptor; Th :T helper; TLR :Toll-like receptor; WT: wild type.

**Beteiligte Forschungseinheiten**

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