Recognition of DHN-melanin by the C-type lectin, MelLec, is required for protective immunity to *Aspergillus fumigatus*

Mark H.T. Stappers, Alexandra E. Clark, Vishukumar Aimananda, Stefan Bidula, Delyth M. Reid, Patawee Asamaphan, Sarah E. Hardison, Ivy M. Dambuza, Isabel Valsecchi, Bernhard Kerscher, Anthony Plato, Carol A. Wallace, Raif Yuecel, Betty Hebecker, Maria da Glória Teixeira Sousa, Cristina Cunha, Yan Liu, Ten Feizi, Axel A. Brakhage, Kyung J. Kwon-Chung, Neil A. R. Gow, Matteo Zanda, Monica Piras, Chiara Zanato, Martin Jaeger, Mihai G. Netea, Frank L. van de Veerdonk, João F. Lacerda, António Campos Jr., Agostinho Carvalho, Janet A. Willment, Jean-Paul Latgé and Gordon D. Brown.

Summary

C-type lectin receptors play a crucial role in recognition of fungi and induction of protective antifungal immune responses.

Here, we identify a C-type lectin receptor, Melanin sensing C-type Lectin receptor (MelLec), which is essential for protective immunity to *Aspergillus fumigatus*.

MelLec:

- Recognizes fungal DHN-melanin.
- Is expressed on CD31⁺ endothelial cells in various murine tissues.
- Plays a crucial role in controlling systemic *A. fumigatus* infection in a murine model.
- Polymorphism Gly26Ala, when present in donor cells, increases the susceptibility of stem-cell transplant patients to disseminated aspergillosis.

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MelLec recognizes DHN-melanin in conidial spores of *Aspergillus fumigatus*

Figure 1. Histograms (a) and immunofluorescence micrographs (b) using Fc-MelLec to detect ligands on wild-type *A. fumigatus* conidia and following conidial swelling and germination over time. Histograms (c) and immunofluorescence micrographs (d) using Fc-MelLec to detect ligands on rodlet-deficient, melanin-containing ($\Delta rodA$) or melanin-deficient ($\Delta pksP$) *A. fumigatus* conidia, as indicated. Detection of MelLec ligands on *A. fumigatus* DHN-melanin synthesis pathway mutants (e), and DHN-melanin intermediate YWA1 (f) by ELISA.

Acknowledgements

MelLec is expressed on endothelial cells

Figure 2. a-b, Flow cytometric analysis of MelLec expression on live cell populations in the murine lung, as indicated. c, Immunofluorescence microscopy of naïve lung tissue from wild-type and MelLec^{-/-} mice stained with αMelLec (green).

MelLec^{-/-} mice display increased susceptibility to invasive aspergillosis

Figure 3. a, Survival of mice following intravenous (i.v.) infection with 10⁶ *A. fumigatus* wild-type conidia. Tissue fungal burdens (b) and brain cytokine levels (c) in mice 4 days after i.v. infection with 10⁶ *A. fumigatus* conidia. d, Survival of mice following i.v. infection with 10⁶ melanin-deficient ($\Delta pksP$) *A. fumigatus* conidia.

MelLec SNP increases risk of aspergillosis

Figure 4. a, Cumulative incidence analysis of invasive aspergillosis after stem-cell transplantation according to donor (wild-type, n=238; SNP allele, n=72) or recipient (wild-type, n=228; SNP allele, n=80) *CLEC1A* rs2306894 genotypes. b, Inflammatory cytokine production in monocyte-derived macrophages, following stimulation with *A. fumigatus* conidia (wild-type, n=14; SNP allele, n=5).