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Defining the early *in vivo* immune response after pulmonary *Aspergillus* challenge under different immune suppressive regimens

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Background: The number of patients with immune suppression is steadily increasing due to various clinical therapies that require administration of immunosuppressive drugs as it is the case for patients undergoing allogenic hematopoietic stem cell or solid organ transplantation and patients with autoimmune conditions. Other disease conditions such as cancer, retroviral infections and genetic immune disorders also compromise the immune system. Fungal infections with the invasive mold *Aspergillus* fumigatus cause high morbidity and mortality in these clinical situations. The degree of immune suppression influences the severity of A. fumigatus infections. Furthermore, how virulence factors impact the immune response and consequently the outcome of infection remains elusive. Therefore, a better understanding of immune cell responses in various degrees of immune suppressive states following infection with virulent and attenuated A. fumigatus strains is required.

Methods: To investigate the immune cell response under different immune suppressive regimens, we employed corticosteroid treated and cyclophosphamide treated leukopenic mouse models of invasive aspergillosis. We challenged immune competent, corticosteroid treated and leucopenic mice with 106 A. fumigatus virulent wild type or avirulent melanin layer deficient pksP mutant conidia. The immune cell recruitment in post-infection early and late time points (4h, 16h and 40h) was quantified using FACS analysis and histology. We utilized dynamic in situ multi-photon microscopy to corroborate our findings and to visualize the dynamic interactions between eGFP labeled immune cells and growing td tomato transgenic A. fumigatus in the lung under ex vivo conditions.

Results and conclusion: Innate and adaptive immune cell populations significantly decreased after corticosteroid treatment. Infection of these mice with A. fumigatus wild type conidia resulted in a significant early (4 h) recruitment of neutrophils, alveolar macrophages, conventional macrophages, monocytes and eosinophils. However, at 16 h and 40 h after infection, immune cells decreased below steady state levels. In the leukopenic model, most of the immune cells disappeared from the lungs. However, at 4h after A. fumigatus infection reduced, but significant numbers of neutrophils, macrophages and monocytes were recruited to the lungs. In contrast to the corticosteroid model, the neutrophil recruitment persisted even at 16 h and 40 h after infection in leukopenic mice, even if immune cells decreased below the steady state levels. There was no significant recruitment of DCs, NK- and T cell subpopulations in both models. Surprisingly, the immune cell recruitment did not differ after infection with WT or the avirulent pksP conidia after 4h and 16h.This data suggest that the lack of melanin in pksP A. fumigatus mutants does not impact immune cell recruitment, but rather acts via suppression of reactive oxygen intermediates produced by immune cells. Taken together, these results demonstrated that myeloid cells are crucial for defense against A. fumigatus infections under immune suppression conditions.

Biography

Natarajaswamy Kalleda completed his Masters in biotechnology from Osmania University, Hyderabad, India. He worked as an ICMR-Senior Research Fellow in University of Delhi for couple of years and at present he is working in Wuerzburg University Hospital, Wuerzburg, Germany. He has background in molecular biology and immunology of fungal infections.

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