The role of IL-32 in the innate host response against *Candida albicans*

Martin Jaeger^{1*}, Jessica C. Dos Santos^{1,2*}, Bas Heinhuis¹, Rodrigo Saar-Gomes², Mark Gresnigt¹, Michelle Damen¹, Fatima Ribeiro-Dias², Melissa Johnson³, Yang Li⁴, Vinod Kumar⁴, Charles A. Dinarello^{1,5}, Mihai G. Netea¹, Leo A.B Joosten^{1,2}

¹Department of Internal Medicine and Radboudumc Center for Infectious Diseases (RCI), Radboud University Medical Center, Nijmegen, The Netherlands. ²Instituto de Patologia Tropical e Saúde Pública, Universidade Federal de Goiás, Goiânia, Goiás, Brazil. ³Division of Infectious Diseases, Duke University School of Medicine, Durham, North Carolina, USA. ⁴University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, The Netherlands. ⁵Department of Infectious Diseases, University of Colorado, Denver, Denver, Colorado, USA.

Introduction:

Infections with *Candida albicans* are still a major problem in immunocompromised and hospitalized patients leading to a large number of death and costs for health care systems worldwide. Extensive genetic and population wide studies have identified important components in *Candida* host response pathways that are dysregulated that are responsible for disease susceptibility. The intracellular interleukin (IL)-32 has recently been described to be important in several bacterial infections but nothing is known about its role in fungal infections. By using a combined genetic and in vitro approach we investigated the role of IL-32 in the host response against *Candida*.

Results:

Polymorphism in IL-32 influences *Candida* induced cytokines

Figure 1: Influence of IL-32 polymorphism on *Candida* induced cytokines (A) T cell cytokines, (B) Monocyte derived cytokines

Recombinant IL-32γ increases *Candida* induced cytokines and phagocytosis

Figure 2: Influence of recombinant IL-32 on cytokines (A-C) and phagocytosis of *Candida* (D)

Candida induces IL-32 and IL-32γ gets spliced after 7 days

Figure 3: Production of IL-32 protein as well as different IL-32 transcript after (A) 24 hours and (B) 7 days

IL-32γTg mice show increased survival and increase cytokine production in the spleen

Figure 4: Survival curve after lethal systemic *Candida* infection and cytokine production by spleen cells after 24 and 48 hours

Differences in 90-day survival depending on IL-32 genotype

Figure 5: 90 day survival of candidemia patients with different genotypes for rs1555001 in IL-32. Proposed hypothesis of functional effect of genetic variant

Conclusion

- rs1555001 influences *Candida* induced cytokines
- Candidemia patients with TT have diminished IFNγ production
- rIL-32γ increases cytokines and phagocytosis in vitro
- *Candida* induces IL-32 isoforms
- IL-32 does not have direct antimicrobial effect on *Candida*
- IL32γtg mice benefit in compared to control mice in systemic candidiasis model