Evaluating the role of STAT3 in CD4+ T cells in susceptibility to invasive aspergillosis

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INTRODUCTION

• Transcription factor signal transducer and activator of transcription 3 (STAT3) is an important immune regulator that promotes T cell development [1].

• Th17 cells play a critical role in host defense during invasive aspergillosis (IA) by activating transcription STAT3 to induce production of IL17 and IL22, which promote local inflammatory responses [2].

• Patients with mutations in STAT3 (e.g., hyperimmunoglobulin E [Job’s] syndrome) have selective impairment of IL-17 producing Th17 T cells and are prone to Aspergillus infections [3].

• Role of STAT3 deficiency in immunocompromised mice on susceptibility to invasive aspergillosis and mortality is not well delineated.

OBJECTIVE

1. To determine if CD4(STAT3-/-) mice are at a higher risk for developing IA

2. To determine if STAT3 inhibition in CD4 T cells is associated with increase mortality due to IA in CD4(STAT3-/-) mice

METHODS

• CD4(STAT3-/-) mice were generated by breeding pairs obtained from Jackson Laboratories:
  • CD4 Cre mice (STOCK Tg(Cd4-cre)1Cwi/Bflu) 
  • Stat3 flox/flox mice (B6.129S1-Stat3tm1Xyfu/J)

• Four groups of mice were included in the study:
  1. Control (STAT3 fl/fl) – non-immunosuppressed
  2. Control (STAT3 fl/fl) – immunosuppressed
  3. CD4(STAT3-/-) – non-immunosuppressed
  4. CD4(STAT3-/-) – immunosuppressed

• Immunosuppression regimen (cortisone acetate [250 mg/kg], cyclophosphamide [250 mg/kg]) was administered 2 days before infection and 3 days post infection to induce neutropenia.

• Mice were infected with A. fumigatus using an inhalation chamber.

• A subset of mice were sacrificed 3 days post infection to perform lung culture counts, measure cytokines in BAL and plasma; the remaining mice were monitored for 21 days.

RESULTS

Figure 1: Survival of Control and CD4(STAT3-/-) non-immunosuppressed and immunosuppressed mice. N= 10 in each group.

Figure 2: Weights of each group of mice over the course of 21 days. N= 10 in each group.

Figure 3: Homogenized lung culture counts 3 days post infection. N= 5 in each group.

Figure 4: PAS staining of lungs 3 days post infection. Scale bar is 100 μm.

Figure 5: Proinflammatory cytokines in BAL 3 days post infection. N= 5 in each group.

Figure 6: Plasmatic proinflammatory cytokines 3 days post infection. N= 5 in each group.

CONCLUSIONS

• Our results suggest that inhibition of STAT3 in CD4 T cells of mice results in muted Th17 response, decreased production of IL-17, IL-22 and IFNγ in the BAL.

• There was no difference in mortality at 21 days post infection, however there was a trend towards earlier death in CD4(STAT3-/-) mice.

REFERENCES

