Animal models to inform clinical research: vitamin A supplementation combats invasive non-typhoidal Salmonella infection

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Introduction
There is an epidemic of invasive non-typhoidal Salmonella (INTS) infection, with 3.4 million cases and approximately 680,000 deaths occurring annually worldwide (1). Children in sub-Saharan Africa are particularly vulnerable, with a case fatality of 20-25% (1,2). An important risk factor of INTS infection is malnutrition (2). In 2009, the WHO estimated that 190 million million preschool age children were vitamin A deficient (VAD) (3). Animal models of infectious disease are critical for elucidating immunological mechanisms underlying susceptibility and informing next steps in clinical research. Using a mouse model of vitamin A deficiency, our laboratory has found that VAD mice are more susceptible to developing INTS. Importantly, vitamin A supplementation (VAS) improves control of infection. VAS is not new to global health; it is efficacious prevention in vitamin A deficient (VAD) (3). Animal models of infectious disease occurring annually worldwide (1). Children in sub-Saharan Africa and invasive non-typhoidal Salmonella infection and vitamin A deficiency

Granulopoiesis is compromised during invasive non-typhoidal Salmonella infection and vitamin A deficiency

Vitamin A deficiency reduces Slc11a1-mediated neutrophil bactericidal activity

Reactive oxygen species production and intracellular bactericidal activity of neutrophils in cell culture is dependent on vitamin A concentration

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References

Conclusions
• Vitamin A deficiency in mice can be used as a model of how malnutrition compromises the immune response to INTS infection.
• Molecular mechanism: Emergency granulopoiesis is impaired during INTS infection in VAD mice.
• Neutrophils recruited to systemic sites during INTS infection in mice have compromised control of the infection and is dependent on Slc11a1.
• Reactive oxygen species formation is dependent on vitamin A concentration in cell culture.
• Intracellular bactericidal capacity is dependent on vitamin A concentration in cell culture.
• Clinical application: Vitamin A supplementation rescues the immunologic phenotype of INTS infection in VAD mice.

Future directions
Vitamin A supplementation increases survival in VAD mice with INTS

Mouse model of vitamin A deficiency and invasive non-typhoidal Salmonella

A. VAD and INTS timeline

B. Hepatic retinol is decreased in VAD mice

C. Salmonella burden is increased at systemic sites in VAD mice

D. Retinol treatment leads to improved control of Salmonella burden at systemic sites in VAD mice

E. Vitamin A deficiency reduces Slc11a1-mediated neutrophil bactericidal activity

F. Reactive oxygen species production and intracellular bactericidal activity of neutrophils in cell culture is dependent on vitamin A concentration

G. Conclusions

H. Future directions

References

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