RESEARCH ARTICLE SUMMARY

IMMUNOLOGY

Serum amyloid A delivers retinol to intestinal myeloid cells to promote adaptive immunity

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INTRODUCTION: Vitamin A is a lipid-soluble nutrient that is absorbed from the diet by intestinal epithelial cells and converted to retinol. This product of vitamin A metabolism is essential for intestinal adaptive immunity because it directs the development of B and T cells and promotes their recruitment to the intestine. Consequently, vitamin A deficiency confers increased susceptibility to infectious diseases of the intestine.

Intestinal myeloid cells play a central role in the development of vitamin A–dependent intestinal immunity. Certain myeloid cells convert retinol to retinoic acid (RA) and then pass the RA to developing B and T cells. This activates RA-dependent gene expression programs that direct B and T cells to home to the intestine and induces immunoglobulin A (IgA) production by B cells.

RATIONALE: A major unanswered question is how intestinal myeloid cells acquire retinol for conversion to RA. Retinol is lipophilic, necessitating transport by retinol-binding proteins that shield it from the aqueous environment. However, proteins that deliver retinol to myeloid cells remain unidentified.

Serum amyloid A (SAA) proteins are retinol-binding proteins expressed in the intestinal epithelium. Epithelial cell expression of SAAs requires both the intestinal microbiota and dietary vitamin A. SAAs are also produced by the liver and circulate in the serum with bound retinol after systemic bacterial infection. Thus, SAAs are retinol-binding proteins that transport retinol in response to microbial challenge. However, the cellular targets of SAA-retinol complexes are unclear. In this study, we identified a receptor for SAA-retinol complexes that mediates retinol uptake into intestinal myeloid cells. Moreover, we determined how this retinol uptake mechanism affects vitamin A–dependent immunity.

RESULTS: Using biochemical approaches, including chemical cross-linking and mass spectrometry, we identified low-density lipoprotein (LDL) receptor–related protein 1 (LRP1) as a cell surface receptor for SAAs that binds SAA-retinol complexes with high affinity. We showed that LRP1 mediates cell surface binding and the endocytosis of SAA-retinol complexes in cultured cells. In the intestine, the highest levels of LRP1 expression were on $CD11c^{+}$ myeloid cells, which efficiently bound SAA-retinol complexes, thereby internalizing retinol. The physiological roles of SAAs and their LRP1 receptor were identified in vivo using two mouse models: $Saa^{-/-}$ mice with a deletion of the entire *Saa* gene locus and $Lrp1^{\Delta Cd11c}$ mice with a myeloid cell–specific deletion of the *Lrp1* gene. Studies of these mice revealed that SAAs and their LRP1 receptor facilitated retinol uptake by intestinal myeloid cells in vivo and promoted the expression of enzymes that convert retinol to RA. Accordingly, SAAs and myeloid cell LRP1 were required for the development of vitamin A–dependent adaptive immunity, including B and T cell homing to the intestine and IgA production. Finally, we found that SAAs and LRP1 promoted immunity to enteric infection after immunization.

CONCLUSION: We have identified SAAs as retinol-binding proteins that deliver retinol to RA-producing intestinal myeloid cells. SAA-retinol complexes bind to LRP1 on the myeloid cell surface and are endocytosed, providing retinol