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Serum Amyloid A proteins take retinol for a ride

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Abstract

Vitamin A plays pleiotropic roles in the immune system. A recent *eLife* paper by Hooper and colleagues shows that hepatic and intestinal serum amyloid A proteins, which are induced in response to infection, can transport vitamin A metabolites to tissues and thus impact immune responses both locally and systemically.

Dietary vitamin A is essential for the development and maintenance of the mammalian immune system. Vitamin A deficiency has long been associated with increased susceptibility to infections, and vitamin A metabolites, in particular retinoic acid (RA), have been shown to activate innate and adaptive immune cells [1,2]. RA binds to nuclear hormone receptors RAR/RXR, triggering transcription of a variety of genes, and the outcome of this activation can be either pro- or anti-inflammatory, depending on the dose of RA, the target cell and the tissue context. For example, in the presence of TGF- β , RA promotes differentiation of naïve CD4⁺ T cells into T regulatory (Treg) cells while suppressing differentiation into Th17 cells, even in the presence of IL-6 [3]. Hence, vitamin A metabolites impact processes associated with tolerance, immunity and the maintenance of immune homeostasis. While the capacity to metabolize retinol into RA has been attributed to various innate immune cells [1], it has been unclear how retinol levels could be modulated to ensure quick delivery to specific sites during infection, and what molecules mediate this process. Recent findings by Derebe *et al.* [4] identify serum amyloid A proteins (SAA) as potent and inducible retinol carriers, providing insight into the mechanisms that re-route retinol in response to infection.

Vitamin A is absorbed as retinol, β -carotene or retinyl ester by the enterocytes of the small intestine. Due to their hydrophobic nature, these molecules require bile and fatty acids as emulsifiers for efficient absorption. Unaltered carotenoids or retinyl esters can be incorporated into nascent chylomicrons that are secreted by enterocytes and enter circulation via the lymph. These lipoprotein particles mature as they exchange material with high-density and low-density lipoproteins to form chylomicron remnants and deliver newly absorbed vitamin A derivatives to the liver, for central storage, or extrahepatic tissues, which store roughly 30% of retinoids [5]. Thus, the maintenance of systemic retinol levels is classically a function of the liver, which secretes retinol in complex with either retinoid binding proteins (RBPs) or within lipoprotein particles [5].

In studies investigating differential gene expression in intestinal cells upon vitamin A deficiency, Hooper and co-workers observed that levels of SAAs were drastically decreased in mice fed a vitamin A-deficient diet. They inferred that SAAs could participate in retinol transport, as the hydrophobic nature of SAAs implicated these proteins as potential carriers. The authors performed fluorescence-based binding assays revealing that SAA was able to bind vitamin A metabolites with affinity similar to that of RBPs, and with some selectivity: some SAAs bound only retinol, whereas others also bound RA and β -carotene, and only weak binding of retinyl esters was observed. These findings were confirmed by liquid chromatography/mass spectrometry (LC-MS/MS) analyses of blood-derived SAAs collected upon infection. Crystallographic analysis of murine SAA3 revealed a dimer of dimers arrangement that creates a hydrophobic central pocket predicted to fit a retinol molecule. These findings corroborated the 4:1 molar ratio of SAA:retinol found by LC-MS/MS. Since SAAs are also produced by the liver as acute phase proteins in response to bacterial infection [6] and are induced by gut commensal bacteria [7], these retinol transporters may represent an important antimicrobial and immune regulatory pathway. Consistent with this hypothesis, Derebe et al. observed that mice deficient in SAA1 and 2 are more susceptible than wild type mice to *Salmonella* infection [4] while others reported increased susceptibility to chemically induced colitis [8].

These observations may form the basis for new mechanistic hypotheses for regulation of retinol transport. For example, given that SAAs bound retinol strongly but retinyl esters weakly, and that retinol was the only natural SAA ligand recovered *in vivo*, it is possible that intestinal SAAs bind retinol directly in enterocytes prior to its esterification and packaging into chylomicrons. If so, SAAs would thereby be capable of influencing retinol delivery already during initial vitamin A exposure. In addition, the involvement of tryptophan residue 71 (W71) of the SAA hydrophobic core in both SAA dimer formation and retinol binding may suggest a possible structural mechanism for retinol release by SAAs at the target site.

Functionally, these findings also provide new insight into the means by which retinol delivery to certain tissues and cell types could be coordinated in response to infection. Tissues and immune cells with high exposure to SAA and high SAA binding capacity will likely be most receptive to SAA-bound retinol. For example, SAA is found in afferent mesenteric lymph and in association with chylomicrons [9], implying that cells within the mesenteric lymph nodes would have access to high levels of SAA-bound retinol. Likewise, cells with high SAA or lipoprotein particle receptor expression, such as lung CD103⁺ dendritic cells and macrophages expressing TLR2/TLR4/CD36 or SR-B1/LDL-R, would also have an advantage in terms of retinol uptake. Furthermore, a recent report showed that intestinal lamina propria stromal cells depend on commensal bacteria for their expression of RA-converting enzymes, raising the possibility that commensal-induced SAA directly delivers retinol to these cells, thereby influencing the entire lamina propria milieu [10]. Finally, given the high basal expression of SAA4 isoform in the liver, the findings by Derebe et al. indicate that SAAs could contribute to retinol delivery under homeostatic conditions [4].

These findings lead to new questions: are the reported immunomodulatory effects of SAAs [11] dependent on retinol delivery or SAA receptor signaling? Conversely, is retinol

delivery involved in some of the possible detrimental effects of SAAs, such as promotion of atherosclerosis? What is the role of SAA in RA-mediated modulation of the immune system? And finally, can different SAA isoforms and their tissue-specific expression patterns explain the seemingly paradoxical effects of retinoids in immune responses? Answering these questions will provide important insights into the contribution of the retinol carrier function of SAAs to immune homeostasis.

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