Apolipoprotein A-IV in the Follicle-Associated Epithelium: A Further Piece in the Puzzle

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Published online: 19 September 2014
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Apolipoprotein A-IV (apoA-IV) is a 46-kDa exchangeable plasma apolipoprotein, secreted primarily by the intestinal mucosa and to a lesser extent by hepatocytes in humans and in most animals. Since its first description in 1974, a variety of functions has been proposed for apoA-IV, including involvement in the assembly, secretion, and metabolism of lipids, in the regulation of food intake as a satiety factor and modulator of gastric acid secretion, and in the protection against inflammation and atherosclerosis due to its antioxidant properties [1 and references therein]. ApoA-IV is synthesized in villous enterocytes (VE) and assembled to pre-chylomicron transport vesicles in the Golgi complex. The latter contributes to the maturation of pre-chylomicron particles along their vectorial transport to the basolateral surface, prior to secretion into the pericellular spaces adjacent to lymphatic fenestrae [2]. Despite considerable effort, the precise cellular function of apoA-IV in enterocytes has not yet been elucidated.

The follicle-associated epithelium (FAE) is a poorly characterized region of the intestinal mucosa that overlies mucosa-associated lymphoid tissue (e.g., Peyer's patches). The FAE is clearly different from VE, since there is a high density of M (microfold) cells, specialized for antigen sampling and transcytosis of IgA, parallel with the lack of goblet cells and subepithelial myofibroblasts [3 and references therein]. It is unclear whether FAE is comprised in part of predetermined M cell precursors, since the mRNA profile of FAE differs from the transcriptome of M cells or

transcriptome of VE cells [3]. The FAE is considered as a major component of mucosal immune response.

In this issue of *Digestive Diseases and Sciences*, Tokuhara et al. [4] provide evidence that apoA-IV mRNA and protein are constitutively expressed in cells of the FAE, but absent in M cells in the mouse small intestine. Moreover, mice strongly express apoA-IV protein in the jejunal VE before weaning, but surprisingly not in chow-fed young (3-week-old) or adult (7-week-old) mice [4]. In addition to protein expression in the FAE, apoA-IV mRNA is expressed in jejunal VE during development before weaning, which continuously declines after weaning [4]. In adult mice, the mRNA expression of apoA-IV is largely restricted to the FAE and to the tips of jejunal VE [4].

A monoclonal antibody generated by the authors against mouse FAE recognized apoA-IV with high specificity [4], serving as a valuable and unique tool for apoA-IV protein localization, which had not been reported previously, due to lack of antibody specificity [1, 4 and references therein].

Considering the recent findings of Tokuhara et al. [4], the amount of apoA-IV expression in adult mouse VE is most likely very low in the basal or fasting state, with rapid induction following lipid ingestion, consistent with apoA-IV expression in the VE of suckling mice [4], and with the extensive regulation of apoA-IV by nutritional and hormonal factors such as the fat in breast milk [1 and references therein].

Constitutive, age-independent expression of apoA-IV mRNA and protein in the mouse FAE is an important novel finding of Tokuhara et al. [4], adding a further element to the characterization of apoA-IV and to adjacent non-M cells in the FAE. The expression of apoA-IV is not mandatory for the organogenesis of Peyer's patches, as apoA-IV-deficient mice (global knockout) have morphologically intact Peyer's patches [4] and develop no major

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Fig. 1 Scheme of the cellular complexity and the potential role of apoA-IV in follicle-associated epithelium

immunodeficiency [5]. Additional studies of how apoA-IV might influence the biogenesis or differentiation of M cells in the FAE, or the “fine tuning” of Peyer’s patches, for instance, in cell- or tissue-specific apoA-IV deficiency (flox) or knockdown approaches, might be of interest.

One important question that needs to be addressed is the functional significance of apoA-IV expression in the FAE, especially in the apoA-IV-positive cells surrounding M cells. A prior analysis of the molecular interactions with apoA-IV [6] might help further clarify this issue: apoA-IV may contribute to the stability of junctional integrity in FAE through its interaction with α -catenin [6] and thus promote or inhibit the differentiation of adjacent M cells, influence the permeability of FAE for luminal commensal or pathogenic bacteria to induce specific immune responses in Peyer’s patches, or modulate the extension of dendrites of specific antigen-presenting cells in the dome (Fig. 1). ApoA-IV may also function in the VE as intracellular adaptor or chaperone through its interaction with apolipoprotein B-48 (apoB), which contributes to the proper assembly of chylomicrons. In this respect, apoA-IV might work as a cytoplasmic adaptor for metabolic and likely also for immunologic learning in the intestine, as previously postulated by Schmitz and Langmann [7]. The cell cycle of FAE or VE may be influenced by apoA-IV through its interaction with cyclin C [6].

A further possibility is that apoA-IV is actively secreted from FAE, acting on the neighboring immune cells or FAE as a paracrine or autocrine modulator, respectively (Fig. 1). In

this situation, the factors contributing to apoA-IV secretion from FAE have yet to be identified, with Toll-like receptors (TLRs) likely candidates. Expression of TLR2, TLR5, and TLR9 mRNA and protein was reported recently at apical and basolateral sites of the FAE in mice [8]. Endogenous apolipoprotein A-I (apoA-I), a close molecular relative of apoA-IV, is actively secreted from human macrophages in response to Toll-like receptor-4 signaling, stabilizing lipid rafts and the ATP-binding cassette transporter A1 (ABCA1), one of the major mediators of cellular lipid efflux [9]. Since apoA-IV was evolutionarily derived by duplication of the apoA-I gene, with both located in a common gene cluster on human chromosome 11, these apolipoproteins share many properties [10 and references therein]. Thus, apoA-IV may also be secreted from FAE, modulating diverse cellular functions from the extracellular site through receptor interactions and signaling mechanisms.

In summary, Tokuhara et al. [4] have advanced the field by identifying constitutive apoA-IV expression in FAE and by demonstrating age-dependent apoA-IV expression in VE, thus opening up new opportunities for understanding apoA-IV actions in the intestinal mucosa.

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