The vitamin A metabolite all-trans retinoic acid (RA) plays a key role in innate and adaptive immune responses. RA is produced by gut-associated dendritic cells (DC), stromal cells and intestinal epithelial cells, and it acts in a positive feedback loop in DC to induce its own synthesis [1]. RA is critical for generating α4β7⁺ CCR9⁺ gut-tropic lymphocytes and intestinal IgA antibody-secreting cells [1]. Moreover, RA modulates T_{REG}, Th1, Th2 and Th17 differentiation [1]. Recent work indicates that RA is required for establishing oral immune tolerance by inducing gut-tropic T_{REG} [2, 3]. Interestingly, microbiota-specific T_{REG} in colon do not appear to require RA, but depend on short-chain fatty acids (SCFA) acting on the G protein-coupled receptor GPR43 [4]. Moreover, T_{REG} do not need CCR9 to home to the colon, but rely on GPR15 [5], which is upregulated by SCFA [4]. Thus, the mechanisms governing intestinal tolerance to dietary antigens in the upper digestive tract substantially differ from those controlling tolerance to the microbiota in the colon, with RA and SCFA playing key complementary roles in their respective compartments (fig. 1).
Fig. 1. Complementary roles of RA and SCFA in small bowel and colon immune tolerance. RA produced by CD103+ MLN-DC induces α4β7 and CCR9 on T cells, and it potentiates TGF-β-driven T\(_{\text{REG}}\) induction. Gut-tropic T\(_{\text{REG}}\) reach the small intestine (SI) lamina propria (LP), where they expand and become IL-10-producing T\(_{\text{REG}}\) able to suppress proinflammatory responses against dietary antigens. In the colon, T\(_{\text{REG}}\) are specific vs. microbiota antigens, and their homing to this compartment relies on GPR15. SCFA (fermentation products from the commensal microbiota) and the receptor GPR43 are critical to generate and expand colonic T\(_{\text{REG}}\). Moreover, SCFA induce GPR15, hence contributing to T\(_{\text{REG}}\) homing to the colon. While SI-LP T\(_{\text{REG}}\) originate upon T cell activation in mesenteric lymph nodes (MLN), it is unclear where colon T\(_{\text{REG}}\) are generated, although recent data suggest that a large number of microbiota-specific T\(_{\text{REG}}\) might, unexpectedly, originate in the thymus [6].

References