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Dietary and commensal derived nutrients: Shaping mucosal and systemic immunity

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Abstract

The intestine serves as the primary site of nutrient absorption in the body while also harboring the highest burden of commensal microflora and representing a major portal of pathogen exposure. As such, the immune network of the intestine relies on both dietary and commensal derived signals to guide appropriate function. Recent advances highlight the role of dietary derived nutrients and commensal derived metabolites in shaping gastrointestinal immunity. In particular, Vitamin A has been shown to have dominant and pleiotropic effects in the intestine. In addition, dietary derived AHR ligands and commensal derived metabolites are now emerging as important players in mucosal immunity. Thus nutrition, commensal microflora and the mucosal immune system are all intimately connected.

Introduction

The gastrointestinal (GI) tract is charged with a difficult task: it must absorb nutrients while simultaneously establishing détente with commensal microflora and defending against invading pathogens. Critical to achieving this task is the immune network of the GI tract, which is home to one of the largest reservoirs of immune cells in the body [1]. Contained within this complex immunologic network of the GI tract are highly specialized antigen presenting populations, a large population of IgA secreting plasma cells, and an abundance of CD4+ T regulatory (Treg) and Th17 polarized T cells [2]. All of these factors work in concert to promote barrier function of the GI tract and to maintain tolerance to food and commensal bacteria. Our understanding of the intestinal immune system has grown immensely over the past decade. With this understanding has come a greater appreciation of the dominant signals immune cells are exposed to in the GI tract. In addition to tonic commensal microflora derived signals, the intestinal immune system appears to be uniquely well equipped to respond to dietary derived factors and micronutrients and, in some cases, relies on these nutritional cues for its function [3].

Nutrient deficiencies underscore the importance of micronutrients in regulation of mucosal immunity. One dietary micronutrient that has emerged as a critical mediator of mucosal immune responses is Vitamin A and, particularly, its metabolite retinoic acid (RA) [4]. Vitamin A deficiency, one of the most common micronutrient deficiencies [5], is associated

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with higher rates of mortality [6], while supplementation of deficient children with Vitamin A is able to reduce mortality [7]. Although the importance of Vitamin A in supporting mucosal immunity has long been appreciated, recent findings have enhanced our understanding of the diverse mechanisms by which Vitamin A accomplishes this task and its contextual role in promoting immunity. As well, additional signals controlling immune function in the GI tract have come to light consisting of dietary derived factors and commensal metabolites.

Vitamin A: A keystone dietary micronutrient for intestinal immunity

Vitamin A is a fat-soluble essential micronutrient obtained from foods containing either vitamin A precursors in the form of carotenoids or from vitamin A itself in the form of retinyl esters [8]. After absorption, retinyl esters are hydrolyzed into retinol in the liver for release into the circulation or are recycled into the gut via bile drainage. Retinol taken up by cells is converted to retinoic acid (RA) by sequential oxidation by alcohol dehydrogenases (ADH) and retinaldehyde dehydrogenases (RALDH). RA is mainly generated in the all-trans isoform [8] and, therefore, the immunological effects of this compound are the focus of current research efforts. Recent advances in understanding the role of RA have uncovered some of the relevant sources of RA and the signals necessary for RA production by these cells. As well, the complex and contextual role of RA continues to be clarified.

Although RA is constitutively present in serum at low levels [9], RALDH induction is subject to tight regulation and is controlled by environmental cues. Many cell types in the intestine are capable of synthesizing RA, including epithelial, stromal and dendritic cells. An important source of RA in the lamina propria of the intestine is thought to arise from a specialized subset of CD103+ migratory DCs with high basal expression of Aldh1a2, encoding the enzyme responsible for RA generation, RALDH2 [10–12]. Initial reports indicated that RA expression could be driven by the cytokines GM-CSF and IL-4 [13]. Subsequently, TLR signaling was shown to promote RALDH2 expression in both mucosal and peripheral DCs [14]. Another factor that has been shown to promote RALDH expression in intestinal DCs is beta-catenin [15]. Interestingly, RA itself has been shown to re-enforce RALDH2 expression in DCs [16,17]. These data suggest a model in which gut specific factors (cytokines, TLR ligands, or RA) prime DCs to generate RA, which is then sensed by DCs in order to re-enforce RA production.

Retinoic acid (RA) came into focus as an important factor for promoting intestinal immunity when it was found to directly induce the gut homing markers α4β7 and CCR9 on both T cells and B cells [12,18]. These studies highlighted the importance of RA in specifically supporting mucosal immunity by controlling the trafficking of responding cells. Indeed, the generation of key components of the mucosal immune system: IgA+ plasma cells, CD4+ Tregs and Th17 cells are all regulated by RA derived signals. In addition to controlling the tissue tropism of these cells, RA also influences the differentiation of cells towards lineages important for mucosal defense (Figure 1). For instance, RA signaling on B cells results in the selective promotion of intestinal IgA via enhancement of class switching to IgA [18,19]. Notably, vitamin A metabolism plays a central role in the acquisition of oral tolerance, a process that requires peripheral generation of Foxp3+ Treg cells [20,21**]. Mice in which Foxp3+ Treg cells cannot be induced, failed to establish tolerance at mucosal surfaces and develop aberrant Th2 responses in both the lung and GI tract [20]. The extrathymic differentiation of Foxp3+ Tregs in the GI tract is tightly controlled at steady state by the capacity of a specialized population of gut tropic DCs expressing CD103 that have a potent capacity to activate latent TGF-β and produce RA [22–25**]. The effect of RA is not limited to regulatory responses as RA, in a context dependent manner, can promote effector T cell responses. Indeed, vitamin A deficient mice have greatly diminished Th17

composition in their small intestines at steady state [26,27] and lower, physiologic, concentrations of RA can promote the differentiation and trafficking of Th17 cells to the small intestine [26–28]. As well, antigen presenting cells from vitamin A deficient mice are impaired in their ability to secrete IL-6, indicating that RA is important for the functional capacity of DC's to promote Th17 differentiation [29]. Thus, RA can promote both Treg and Th17 lineages in a context specific manner [4].

Recent evidence suggests that retinoic acid may have a more general role in promoting both mucosal and peripheral immunity [29,30**]. Indeed, impaired RARα signaling revealed a cell intrinsic role for RA sensing by naïve CD4+ T cells in order to achieve a proper threshold of TCR signaling and to become fully activated in the context of infection and skin allograft [29,30]. Both of these studies demonstrate that RA synthesis increases during systemic inflammation, likely in order to support various aspects of immune responses including T cell activation. All together, recent work on the multifaceted role of retinoic acid begins to offer a mechanistic explanation for the profound immune deficiencies associated with increased susceptibility to infections and poor vaccine responses observed in vitamin A deficiency.

Notably, several recent studies have begun to apply these findings to clinical settings. Recent work demonstrated that the addition of RA at the time of peripheral vaccination has a profound capacity to increase the accumulation of memory cells in the gut mucosa [31*]. Given the key role of RA in supporting effector responses, the peripheral administration of vaccines with RA provides an opportunity to not only target vaccines to mucosal surfaces, but to utilize RA as a vaccine adjuvant. The role of RA in supporting effector responses during inflammatory settings has also been found to have deleterious effects. In the context of Celiac disease, RA in combination with IL-15 can drive dendritic cell activation and production of IL12/23 p40 [32*]. Such activation results in impaired Treg priming and augmented effector responses to the dietary gluten antigen, gliadin [32]. Given the expanded knowledge of RA in regulating immunity, it will be important to further understand the contextual roles of RA, particularly in clinical settings.

Other dietary micronutrients

Micronutrients are important for systemic immunity and deficiencies lead to immunosuppression and/or immune dysregulation. These include, but are not limited to: iron, folate, zinc, vitamin A, vitamin C, vitamin E [33,34]. Of these, vitamin D has recently been shown to have profound and direct effects on T cell activation [35*]. Notably, vitamin D can control various aspects of intestinal immunity (Figure 1). Intraepithelial lymphocytes of the CD8αα TCRβ+ subset are reduced in Vitamin D receptor (VDR) deficient mice and appear to be developmentally dependent on VDR signaling [36]. Several studies have linked vitamin D deficiency to inflammatory bowel disease (IBD) susceptibility both in mouse studies of vitamin D receptor deficient mice and in correlative studies of IBD patients [37]. Of interest, activated Tregs and effector T cells express high levels of folate receptor 4 (FR4), although a role for folate in influencing Treg function remains unclear [38]. Because of the constant exposure of the GI mucosa to dietary components, animal models of micronutrient deficiencies warrant future exploration. Future studies will need to mechanistically dissect the effects of different micronutrients on the immune system and specifically their impact on mucosal immunity.

Additional dietary and commensal derived substances

Dietary intake, either directly or via its processing by commensal communities, provides a multitude of metabolites with the potential to influence immune function (Figure 1). Additionally, dietary intake of food provides non-nutritive ligands for the immune system as

well. Two recent studies indicate that dietary derived Ayrl Hrydrocarbon Receptor (AHR) ligands from cruciferous vegetables, such as broccoli, may be important signals for intestinal immune development and immune responses [39,40**]. Indeed, AHR deficient mice have a defect in intraepithelial lymphocyte (IEL) development in both skin and intestine [39]. Using diets with low amounts of AHR ligands or enriched in AHR ligands, this study demonstrates that dietary derived AHR ligands control intestinal but not skin IEL development [39]. Complementing these findings, intestinal lymphoid tissue inducer (Lti) populations are developmentally regulated by dietary AHR Ligands and AHR deficient mice are highly susceptible to infection with the attaching effacing intestinal pathogen *Citrobacter rodentium* [40]. These findings further highlight the central role of dietary components in controlling mucosal immunity.

Another node of interaction that is important to consider in the GI tract is the sensing of commensal metabolites by the immune system. An example of such communication is the metabolism of dietary fiber by commensal bacteria of the Bacteroidetes phylum into immunomodulatory short chain fatty acids (SCFA) such as butyrate and acetate [41]. SCFA binding to GPR43 receptor on neutrophils acts to restrain their activation [41]. Consequently, mice lacking GPR43 have augmented inflammatory responses, while exogenous administration of SCFA to wild type mice was clinically beneficial [41].

Interdependence of diet, commensals and immune interactions

Understanding the role of micronutrients in intestinal immune responses requires integration of the complex and intimately linked relationship between diet, commensals and the immune system (Figure 2). A high fat diet is an example of dietary effects on both commensals and immunity. Mice fed a high fat diet have altered commensal communities that not only affect energy harvest, but that can also alter immunity and increase the severity of disease states such as colitis [42–44*]. Additionally, dietary deficiency can alter commensal communities as demonstrated by a study showing that Vitamin A deficient mice have altered commensal communities as well as immune deficits [26].

Immunodeficiency can also have profound effects on nutrient absorption and metabolism. For instance, mice lacking B cells have a dietary malabsorption [45]. Conversely, mice deficient in the receptor for bacterial flagellin, TLR5, have a dysbiotic commensal microflora that leads to increased weight gain and the development of metabolic syndrome [46**]. Further, these metabolic alterations can be transmitted to wild type germ-free mice by colonizing them with gut flora from TLR5 deficient mice [46]. This implies that immunodeficiencies can alter the gut flora’s composition and the metabolic capacity of both the flora and the host.

Children with severe malnutrition represent an example of both immunodeficiency and dietary deficiency coinciding in a clinically relevant and important way. Malnourished children have dramatically altered commensal communities likely with diminished metabolic capacity and impaired ability to promote host energy absorption; a problem that could persist even after refeeding [44,47,48]. Thus, through the measurement of commensal metabolites in healthy states, as in the case of SCFA, the mucosal immune system may be able to monitor the diversity and metabolic function of intestinal commensal communities. Perhaps, appropriate intestinal immunity requires a diversity of signals that are lacking in a malnourished state. Thus, considering the interdependency of these three factors, an important challenge over the next few years will be to develop experimental strategies aimed at defining critical regulators of this complex and interdependent network.

Conclusion and Future directions

Dietary derived substances and commensal metabolites are critical regulators of intestinal immunity. Both homeostasis and response to infection in the GI tract requires the integration of environmental signals derived from commensal bacteria as well as dietary sources. Of these, RA has emerged as a dominant regulator of immune responses in the GI tract as well as systemically. Recent advances have also brought to light the importance of other dietary substances, such as AHR ligands and commensal derived SCFA, in controlling mucosal immune responses. Are these unique examples or does the mucosal immune system respond to the multitude of available dietary cues? It will be important to test the generalizability of these two sets of findings. We could speculate that because the primary role of the gut is food absorption, the immune system of the GI tract is more finely tuned to respond to dietary status than we currently appreciate [49].

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References

1. Mowat AM, Viney JL. The anatomical basis of intestinal immunity. Immunol Rev. 1997; 156:145–166. [PubMed: 9176706]
2. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. Science. 2012; 336:1268–1273. [PubMed: 22674334]
3. Maslowski KM, Mackay CR. Diet, gut microbiota and immune responses. Nat Immunol. 2011; 12:5–9. [PubMed: 21169997]
4. Hall JA, Grainger JR, Spencer SP, Belkaid Y. The role of retinoic acid in tolerance and immunity. Immunity. 2011; 35:13–22. [PubMed: 21777796]
5. Sommer A. Vitamin a deficiency and clinical disease: an historical overview. J Nutr. 2008; 138:1835–1839. [PubMed: 18806089]
6. Underwood BA. Vitamin A deficiency disorders: international efforts to control a preventable “pox”. J Nutr. 2004; 134:231S–236S. [PubMed: 14704325]
7. Rahmathullah L, Underwood BA, Thulasiraj RD, Milton RC, Ramaswamy K, Rahmathullah R, Babu G. Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. N Engl J Med. 1990; 323:929–935. [PubMed: 2205798]
8. Harrison EH. Mechanisms of digestion and absorption of dietary vitamin A. Annu Rev Nutr. 2005; 25:87–103. [PubMed: 16011460]
9. Kane MA, Folias AE, Wang C, Napoli JL. Quantitative profiling of endogenous retinoic acid in vivo and in vitro by tandem mass spectrometry. Anal Chem. 2008; 80:1702–1708. [PubMed: 18251521]
10. Jaensson E, Uronen-Hansson H, Pabst O, Eksteen B, Tian J, Coombes JL, Berg PL, Davidsson T, Powrie F, Johansson-Lindbom B, et al. Small intestinal CD103+ dendritic cells display unique functional properties that are conserved between mice and humans. J Exp Med. 2008; 205:2139–2149. [PubMed: 18710932]
11. Schulz O, Jaensson E, Persson EK, Liu X, Worbs T, Agace WW, Pabst O. Intestinal CD103+, but not CX3CR1+, antigen sampling cells migrate in lymph and serve classical dendritic cell functions. J Exp Med. 2009; 206:3101–3114. [PubMed: 20008524]
12. Iwata M, Hirakiyama A, Eshima Y, Kagechika H, Kato C, Song SY. Retinoic acid imprints gut-homing specificity on T cells. Immunity. 2004; 21:527–538. [PubMed: 15485630]

13. Yokota A, Takeuchi H, Maeda N, Ohoka Y, Kato C, Song SY, Iwata M. GM-CSF and IL-4 synergistically trigger dendritic cells to acquire retinoic acid-producing capacity. Int Immunol. 2009; 21:361–377. [PubMed: 19190084]

14. Wang S, Villablanca EJ, De Calisto J, Gomes DC, Nguyen DD, Mizoguchi E, Kagan JC, Reinecker HC, Hacohen N, Nagler C, et al. MyD88-dependent TLR1/2 signals educate dendritic cells with gut-specific imprinting properties. J Immunol. 2011; 187:141–150. [PubMed: 21646294]

15. Manicassamy S, Reizis B, Ravindran R, Nakaya H, Salazar-Gonzalez RM, Wang YC, Pulendran B. Activation of beta-catenin in dendritic cells regulates immunity versus tolerance in the intestine. Science. 2010; 329:849–853. [PubMed: 20705860]

16. Villablanca EJ, Wang S, de Calisto J, Gomes DC, Kane MA, Napoli JL, Blaner WS, Kagechika H, Blomhoff R, Rosemblatt M, et al. MyD88 and retinoic acid signaling pathways interact to modulate gastrointestinal activities of dendritic cells. Gastroenterology. 2011; 141:176–185. [PubMed: 21596042]

17. Feng T, Cong Y, Qin H, Benveniste EN, Elson CO. Generation of mucosal dendritic cells from bone marrow reveals a critical role of retinoic acid. J Immunol. 2010; 185:5915–5925. [PubMed: 20944006]

18. Mora JR, Iwata M, Eksteen B, Song SY, Junt T, Senman B, Otipoby KL, Yokota A, Takeuchi H, Ricciardi-Castagnoli P, et al. Generation of gut-homing IgA-secreting B cells by intestinal dendritic cells. Science. 2006; 314:1157–1160. [PubMed: 17110582]

19. Suzuki K, Maruya M, Kawamoto S, Sitnik K, Kitamura H, Agace WW, Fagarasan S. The sensing of environmental stimuli by follicular dendritic cells promotes immunoglobulin A generation in the gut. Immunity. 2010; 33:71–83. [PubMed: 20643338]

20. Josefowicz SZ, Niec RE, Kim HY, Treuting P, Chinen T, Zheng Y, Umetsu DT, Rudensky AY. Extrathymically generated regulatory T cells control mucosal TH2 inflammation. Nature. 2012; 482:395–399. [PubMed: 22318520]

21**. Mucida D, Kutchukhidze N, Erazo A, Russo M, Lafaille JJ, Curotto de Lafaille MA. Oral tolerance in the absence of naturally occurring Tregs. J Clin Invest. 2005; 115:1923–1933. The first demonstration of a role for peripheral Treg induction in the acquision of oral tolerance. [PubMed: 15937545]

22. Travis MA, Reizis B, Melton AC, Masteller E, Tang Q, Proctor JM, Wang Y, Bernstein X, Huang X, Reichardt LF, et al. Loss of integrin alpha(v)beta8 on dendritic cells causes autoimmunity and colitis in mice. Nature. 2007; 449:361–365. [PubMed: 17694047]

23. Denning TL, Wang YC, Patel SR, Williams IR, Pulendran B. Lamina propria macrophages and dendritic cells differentially induce regulatory and interleukin 17-producing T cell responses. Nat Immunol. 2007; 8:1086–1094. [PubMed: 17873879]

24**. Sun CM, Hall JA, Blank RB, Bouladoux N, Oukka M, Mora JR, Belkaid Y. Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid. J Exp Med. 2007; 204:1775–1785. These studies were the first to demonstrate a role for intestinal DC derived RA in the induction of Treg cells. [PubMed: 17620362]

25**. Coombes JL, Siddiqui KR, Arancibia-Carcamo CV, Hall J, Sun CM, Belkaid Y, Powrie F. A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. J Exp Med. 2007; 204:1757–1764. These studies were the first to demonstrate a role for intestinal DC derived RA in the induction of Treg cells. [PubMed: 17620361]

26. Cha HR, Chang SY, Chang JH, Kim JO, Yang JY, Kim CH, Kweon MN. Downregulation of Th17 cells in the small intestine by disruption of gut flora in the absence of retinoic acid. J Immunol. 2010; 184:6799–6806. [PubMed: 20488794]

27. Wang C, Kang SG, HogenEsch H, Love PE, Kim CH. Retinoic acid determines the precise tissue tropism of inflammatory Th17 cells in the intestine. J Immunol. 2010; 184:5519–5526. [PubMed: 20400707]

28. Takahashi H, Kanno T, Nakayamada S, Hirahara K, Sciume G, Muljo SA, Kuchen S, Casellas R, Wei L, Kanno Y, et al. TGF-beta and retinoic acid induce the microRNA miR-10a, which targets Bcl-6 and constrains the plasticity of helper T cells. Nat Immunol. 2012; 13:587–595. [PubMed: 22544395]

29**. Hall JA, Cannons JL, Grainger JR, Dos LM, Hand TW, Naik S, Wohlfert EA, Chou DB, Oldenhove G, Robinson M, et al. Essential role for retinoic acid in the promotion of CD4(+) T cell effector responses via retinoic acid receptor alpha. Immunity. 2011; 34:435–447. These studies report that RA synthesis increases during inflammation and RARα signaling is required as a checkpoint in T cell activation. [PubMed: 21419664]

30**. Pino-Lagos K, Guo Y, Brown C, Alexander MP, Elgueta R, Bennett KA, De Vries V, Nowak E, Blomhoff R, Sockanathan S, et al. A retinoic acid-dependent checkpoint in the development of CD4+ T cell-mediated immunity. J Exp Med. 2011; 208:1767–1775. These studies report that RA synthesis increases during inflammation and RARα signaling is required as a checkpoint in T cell activation. [PubMed: 21859847]

31*. Hammerschmidt SI, Friedrichsen M, Boelter J, Lyszkiewicz M, Kremmer E, Pabst O, Forster R. Retinoic acid induces homing of protective T and B cells to the gut after subcutaneous immunization in mice. J Clin Invest. 2011; 121:3051–3061. Administering RA with a peripherally administered vaccine, this study is able to both use RA as an adjuvant and target responses to the intestinal mucosa. [PubMed: 21737878]

32*. DePaolo RW, Abadie V, Tang F, Fehlner-Peach H, Hall JA, Wang W, Marietta EV, Kasarda DD, Waldmann TA, Murray JA, et al. Co-adjuvant effects of retinoic acid and IL-15 induce inflammatory immunity to dietary antigens. Nature. 2011; 471:220–224. Using a mouse model of Celiac disease, this study demonstrates the potentially pathogenic role of RA in contributing to inflammation during disease states. [PubMed: 21307853]

33. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. Nat Rev Immunol. 2008; 8:685–698. [PubMed: 19172691]

34. Savy M, Edmond K, Fine PE, Hall A, Hennig BJ, Moore SE, Mulholland K, Schaible U, Prentice AM. Landscape analysis of interactions between nutrition and vaccine responses in children. J Nutr. 2009; 139:2154S–2218S. [PubMed: 19793845]

35. von Essen MR, Kongsbak M, Schjerling P, Olgaard K, Odum N, Geisler C. Vitamin D controls T cell antigen receptor signaling and activation of human T cells. Nat Immunol. 2010; 11:344–349. [PubMed: 20208539]

36. Bruce D, Cantorna MT. Intrinsic requirement for the vitamin D receptor in the development of CD8alphaalpha-expressing T cells. J Immunol. 2011; 186:2819–2825. [PubMed: 21270396]

37. Sun J. Vitamin D and mucosal immune function. Curr Opin Gastroenterol. 2010; 26:591–595. [PubMed: 20639756]

38. Yamaguchi T, Hirota K, Nagahama K, Ohkawa K, Takahashi T, Nomura T, Sakaguchi S. Control of immune responses by antigen-specific regulatory T cells expressing the folate receptor. Immunity. 2007; 27:145–159. [PubMed: 17613255]

39**. Li Y, Innocentin S, Withers DR, Roberts NA, Gallagher AR, Grigorieva EF, Wilhelm C, Veldhoen M. Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. Cell. 2011; 147:629–640. Using AHR deficient mice and dietary modification of AHR ligand availability, these studies show an important role for dietary AHR ligands in intestinal immunity. [PubMed: 21999944]

40**. Kiss EA, Vonarbourg C, Kopfmann S, Hobeika E, Finke D, Esser C, Diefenbach A. Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles. Science. 2011; 334:1561–1565. Using AHR deficient mice and dietary modification of AHR ligand availability, these studies show an important role for dietary AHR ligands in intestinal immunity. [PubMed: 22033518]

41. Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Artis D, et al. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Nature. 2009; 461:1282–1286. [PubMed: 19865172]

42*. Devkota S, Wang Y, Musch MW, Leone V, Fehlner-Peach H, Nadimpalli A, Antonopoulos DA, Jabri B, Chang EB. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in Il10(−/−) mice. Nature. 2012 This study demonstrates that a shift in commensal bacteria on a high fat diet results in an increased incidence of colitis in the IL10 deficient mouse model of IBD.

43. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006; 444:1022–1023. [PubMed: 17183309]

44. Monira S, Nakamura S, Gotoh K, Izutsu K, Watanabe H, Alam NH, Endtz HP, Cravioto A, Ali SI, Nakaya T, et al. Gut microbiota of healthy and malnourished children in bangladesh. Front Microbiol. 2011; 2:228. [PubMed: 22125551]

45. Shulzhenko N, Morgun A, Hsiao W, Battle M, Yao M, Gavrilova O, Orandle M, Mayer L, Macpherson AJ, McCoy KD, et al. Crosstalk between B lymphocytes, microbiota and the intestinal epithelium governs immunity versus metabolism in the gut. Nat Med. 2011; 17:1585–1593. [PubMed: 22101768]

46*. Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, Sitaraman SV, Knight R, Ley RE, Gewirtz AT. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science. 2010; 328:228–231. In the absence of TLR5 there is a shift in commensal microflora in the intestine that leads to metabolic syndrome and can be transmitted to wild type germ free mice via the commensal bacteria. [PubMed: 20203013]

47. Gordon JI, Dewey KG, Mills DA, Medzhitov RM. The human gut microbiota and undernutrition. Sci Transl Med. 2012; 4:137ps112.

48. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, Baldassano RN, Anokhin AP, et al. Human gut microbiome viewed across age and geography. Nature. 2012; 486:222–227. [PubMed: 22699611]

49. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, Pettersson S. Host-gut microbiota metabolic interactions. Science. 2012; 336:1262–1267. [PubMed: 22674330]

50. Yuk JM, Shin DM, Lee HM, Yang CS, Jin HS, Kim KK, Lee ZW, Lee SH, Kim JM, Jo EK. Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin. Cell Host Microbe. 2009; 6:231–243. [PubMed: 19748465]

51. Vaishnava S, Yamamoto M, Severson KM, Ruhn KA, Yu X, Koren O, Ley R, Wakeland EK, Hooper LV. The antibacterial lectin RegIIIgamma promotes the spatial segregation of microbiota and host in the intestine. Science. 2011; 334:255–258. [PubMed: 21998396]

52. Sonnenberg GF, Monticelli LA, Alenghat T, Fung TC, Hutnick NA, Kunisawa J, Shibata N, Grunberg S, Sinha R, Zahm AM, et al. Innate lymphoid cells promote anatomical containment of lymphoid-resident commensal bacteria. Science. 2012; 336:1321–1325. [PubMed: 22674331]

53. Kawamoto S, Tran TH, Maruya M, Suzuki K, Doi Y, Tsutsui Y, Kato LM, Fagarasan S. The inhibitory receptor PD-1 regulates IgA selection and bacterial composition in the gut. Science. 2012; 336:485–489. [PubMed: 22539724]

54. Suzuki K, Meek B, Doi Y, Muramatsu M, Chiba T, Honjo T, Fagarasan S. Aberrant expansion of segmented filamentous bacteria in IgA-deficient gut. Proc Natl Acad Sci U S A. 2004; 101:1981–1986. [PubMed: 14766966]

55. Salzman NH, Hung K, Haribhai D, Chu H, Karlsson-Sjoberg J, Amir E, Teggatz P, Barman M, Hayward M, Eastwood D, et al. Enteric defensins are essential regulators of intestinal microbial ecology. Nat Immunol. 2010; 11:76–83. [PubMed: 19855381]

Highlights

- The diet and dietary derived substances have profound influence on immune responses
- Vitamin A is a keystone dietary micronutrient of the GI tract
- Retinoic Acid is important for promoting effector as well as regulatory responses
- A diverse array of dietary components and commensal metabolites impact intestinal immunity
- Diet, immunity and commensal microflora are interdependent

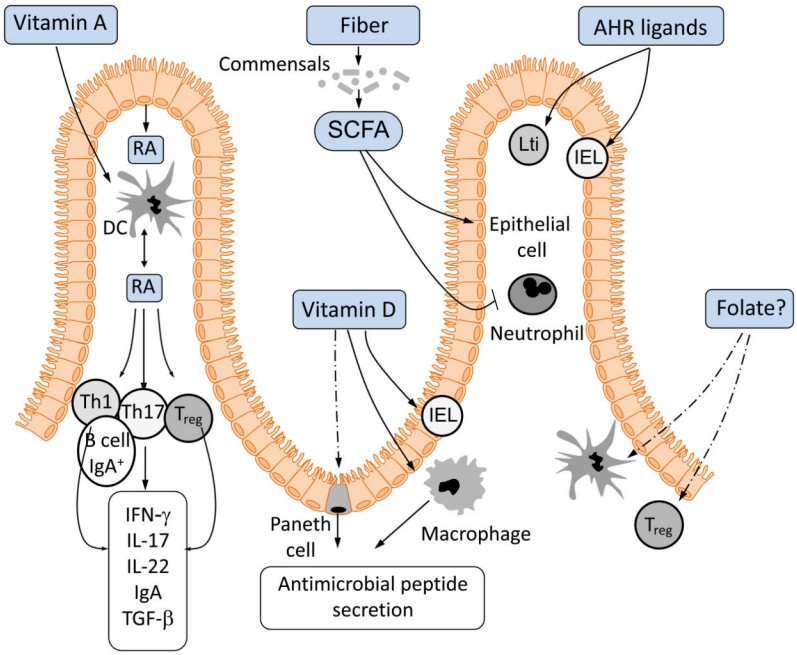

Figure 1. Dietary derived influences on intestinal immunity

Dietary derived factors and nutrients have dominant influences on intestinal immunity. Vitamin A derived retinoic acid can act either on T cells or dendritic cells to promote mucosal immune responses. Vitamin D has been shown to promote IEL development and macrophage antimicrobial peptide secretion [50,36]. Dietary derived AHR ligands regulate IEL maintenance and Lti development[39,40]. Fiber contained in the diet promotes commensal bacteria metabolism of short chain fatty acids (SCFA) which restrain neutrophil function and reinforce epithelial barrier [3,41]. Folate receptor is expressed on immune cells of the GI tract, but the role of folate sensing remains unclear [38].

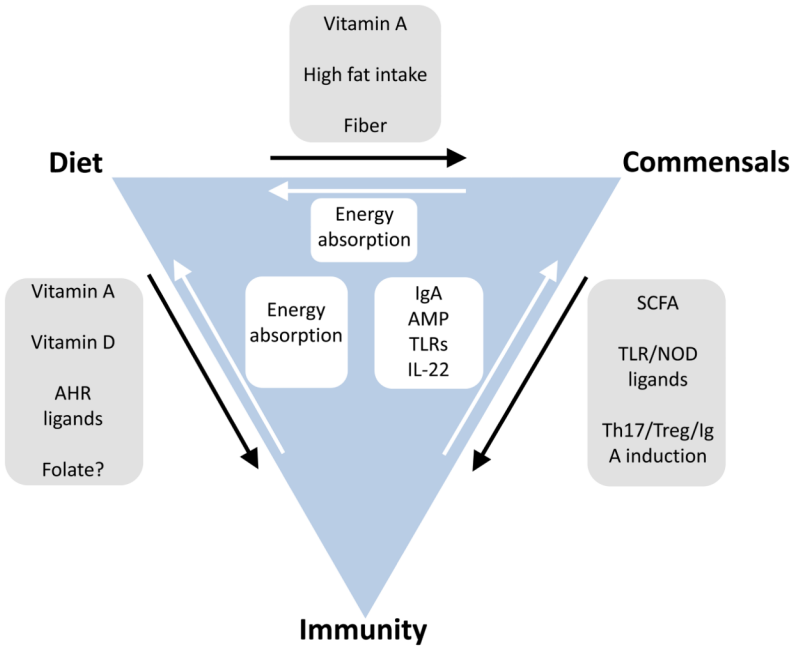

Figure 2. Interdependence of diet, immune and commensal interactions

Evidence now exists for bidirectional communication between the three key factors in the GI tract: Diet, immuninty and commensal microflora. Diet can have profound influences on the immune system (Vit A, Vit D, AHR ligands and Folate), while immunodeficiency impairs energy absorption [45]. Diet also has dominant influence on the composition and metabolic capacity of commensal bacteria, while this, in turn, influences nutrient absorption and energy harvest [43]. The immune system is able to exert control over both commensal composition and localization via recognition of TLR5 ligands and secretion of IL-22 as well as effector mechanisms including IgA production and paneth cell derived antimicrobial peptides (AMP), RegIIIγ and alpha defensins [46,51–55]. Conversely, commensal signals are critical for development and maintenance of the intestinal immune system including the production of short chain fatty acids (SCFA), activation of innate immunity via NOD and TLR ligands and the induction of CD4+ T cell and IgA+ B cell responses [2,41].