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FIELD OF VISION

Tryptophan: A gut microbiota-derived metabolites regulating inflammation

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Abstract

Inflammatory bowel diseases (IBD), which comprise Crohn's disease and ulcerative colitis, are chronic intestinal disorders with an increased prevalence and incidence over the last decade in many different regions over the world. The etiology of IBD is still not well defined, but evidence suggest that it results from perturbation of the homeostasis between the intestinal microbiota and the mucosal immune system, with the involvement of both genetic and environmental factors. Genome wide association studies, which involve large-scale genome-wide screening of potential polymorphism, have identified several mutations associated with IBD. Among them, *Card9*, a gene encoding an adapter molecule involved in innate immune response to fungi (*via* type C-lectin sensing) through the activation of IL-22 signaling pathway, has been identified as one IBD susceptible genes. Dietary compounds, which represent a source of energy and metabolites for gut bacteria, are also appreciated to be important actors in the etiology of IBD, for example by altering gut microbiota composition and by regulating the generation of short chain fatty acids. A noteworthy study published in the June 2016 issue of *Nature Medicine* by Lamas and colleagues investigates the interaction between *Card9* and the gut microbiota in the generation of the microbiota-derived tryptophan metabolite. This study highlights the role of tryptophan in dampening intestinal inflammation in susceptible hosts.

Key words: Intestinal inflammation; Tryptophan; Microbiota

Core tip: A noteworthy article published in Nature Medicine by Lamas and colleagues highlights the role of tryptophan, a microbiota-derived metabolite, in reducing inflammation in the gut. This commentary puts in perspective the main results from this study.

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COMMENTARY ON HOT TOPICS

The human intestinal tract harbors a complex community including 100 trillion of microbes, referred as intestinal microbiota. This diverse microbial ecosystem provides benefits to the host, essentially through its role in energy metabolism and immunity. However, perturbations of gut microbiota (termed dysbiosis) is associated with several disorders, including inflammatory bowel disease (IBD) and metabolic syndrome (obesity-associated diseases)[1]. IBD arise as a complex interaction between host genetic factors, mucosal immune system, intestinal dysbiosis, and environmental factors among which dietary compounds being increasingly appreciated in the onset of inflammatory related disorders. Unraveling the complex crosstalk between these factors arise as a challenge for the understanding and treatment of these disorders. A study published in the June 2016 issue of Nature Medicine by Lamas *et al*[2] made significant progress in this area by investigating how a gene predisposing to IBD (*Card9*, encoding the caspase recruitment domain-containing protein 9) leads to a colitogenic microbiota by impairing its ability to generate tryptophan-derived metabolite.

In their study, the authors reported that the deletion of *Card9* gene, a central component of the innate antifungal immune response, render mice more prone to chemically-induced colitis by dextran sulfate sodium (DSS)[2]. This report strengthens previous studies conducted by others and identifying CARD9 as a gene predisposing to IBD in humans[3-5]. Lamas *et al*[2] also demonstrated that *Card9* knockout mice (*Card9*$^{-/-}$) display alteration of immune-related signaling pathways in the colon, with a strong decrease in interleukin-22 (IL-22) production. The authors evidenced a shift in the bacterial communities and alterations in the composition of the fungal microbiota in Card9$^{-/-}$ mice. Complex inter-kingdom relationships exist in the gut microbiota, suggesting a possible role of CARD9 in shaping the bacterial and fungal communities and required to control fungi during colitis. To decipher the mechanism of such colitis susceptibility and the involvement of gut microbiota in the onset of colitis, the authors use a model of microbial transplantation to germ-free recipient animals, and showed that transfer of colitic-associated microbiota of *Card9*$^{-/-}$ susceptible hosts were sufficient to transferred colitis susceptibility and IL-22 cytokine production impairment in germ-free wild type (*Card9* sufficient) recipients. Those data strengthen the essential role played by the intestinal microbiota, bacteria but also fungi, in triggering intestinal inflammation following Card9 impairment[2].

Further analysis revealed that the colitic-associated microbiota of *Card9*$^{-/-}$ mice is characterized by the absence of bacteria metabolizing tryptophan (an essential amino acid, whose intake is through the diet) into indoles derivatives, such as *Lactobacillus reuteri* and *Allobaculum* sp. Indoles derivatives are ligands for the aryl hydrocarbon receptor (AHR) that can drives local production of IL-22 by innate lymphoid cells and T-cells[6]. Importantly, the authors described that the treatment of *Card9*$^{-/-}$ susceptible animals with an AHR agonist [(*i.e.,* 6-Formylindolo(3,2-b) carbazole named FICZ] was sufficient to restore a normal level of IL-22 production and to protect mice from DSS-induced colitis. Previous studies focusing on the amino acid tryptophan demonstrated that mice fed with a low-tryptophan diet became susceptible to chemically induced inflammation[7] and, conversely, mice or piglets fed with a tryptophan supplemented diet have a reduced inflammation and a decreased severity of DSS-induced colitis[8,9].

As a therapeutic strategy, the authors next postulated that altering the intestinal microbiota in genetically susceptible host so as to increase its ability to generate AHR ligands could protect from intestinal inflammation. Thus, the authors demonstrated that supplementation with three commensal *Lactobacilllus* strains with high tryptophan-metabolic activities was sufficient to restore intestinal IL-22 production and to reverse the colitis susceptibility observed in susceptible *Card9*$^{-/-}$ mice. While previous studies have highlighted how diet can affect the microbiota in a detrimental way, such as the consumption of milk-fat-derived diet that lead to a bloom of pathobiont (*i.e., Bilophila wadsworthia*) and colitis in Il10$^{-/-}$ mice[10]; the study from Lamas *et al*[2] is a good example of the positive interplay between diet and the intestinal microbiota leading to the generation of microbial metabolites that play a central role in the protection against intestinal inflammation.

Finally, in their study, Lamas *et al*[2] further corroborated the results obtained in mice with the analysis of samples from IBD patients, and demonstrated that such patients have a reduced fecal AHR activity and fecal levels of tryptophan. The authors showed that these reductions correlate with *CARD9* polymorphism. These important findings consolidate the prominent role of dietary components and microbial-generated metabolites in mediating inflammation-related disorders. Tryptophan appears to be an important amino acid in IBD patients since they have lower levels of serum and fecal tryptophan compared to healthy subjects[2,11]. In light of the close relationship occurring between the intestinal microbiota and dietary intake, such data further highlight the need of controlling both macro- and micro-nutrients consumption in IBD patients with genetic predisposition.

In the same issue of Nature Medicine, an additional study by Rothhammer *et al*[12] also expand the substantial effect of tryptophan in regulating inflammation, by focusing their study on the central nervous system

(CNS), and providing evidence on the significant role of the bidirectional communication between the gut microbiota and the brain. The authors found that mice fed with a tryptophan-deficient diet have exacerbated CNS inflammation, corroborating the results from Lamas *et al*[2]. These two reports support a potential probiotic strategy, wherein tryptophan-catabolizing *Lactobacillus* strains able to enhance AHR activity that can further beneficially impact the immune system through IL-22 production. Further exploration of possible manipulations of the gut microbiota through dietary modulations by a tryptophan-enriched diet or by re-shaping the microbiota *via* targeting specific populations of bacteria, for example by favoring the tryptophan-producing bacteria or by reducing its pro-inflammatory potential, will provide novel insights into the development of individual targeted approaches that can be harnessed to prevent and/or treat IBD patients.

REFERENCES

1 **Rooks MG**, Garrett WS. Gut microbiota, metabolites and host immunity. *Nat Rev Immunol* 2016; **16**: 341-352 [PMID: 27231050 DOI: 10.1038/nri.2016.42]

2 **Lamas B**, Richard ML, Leducq V, Pham HP, Michel ML, Da Costa G, Bridonneau C, Jegou S, Hoffmann TW, Natividad JM, Brot L, Taleb S, Couturier-Maillard A, Nion-Larmurier I, Merabtene F, Seksik P, Bourrier A, Cosnes J, Ryffel B, Beaugerie L, Launay JM, Langella P, Xavier RJ, Sokol H. CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. *Nat Med* 2016; **22**: 598-605 [PMID: 27158904 DOI: 10.1038/nm.4102]

3 **Jostins L**, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, Lee JC, Schumm LP, Sharma Y, Anderson CA, Essers J, Mitrovic M, Ning K, Cleynen I, Theatre E, Spain SL, Raychaudhuri S, Goyette P, Wei Z, Abraham C, Achkar JP, Ahmad T, Amininejad L, Ananthakrishnan AN, Andersen V, Andrews JM, Baidoo L, Balschun T, Bampton PA, Bitton A, Boucher G, Brand S, Buning C, Cohain A, Cichon S, D'Amato M, De Jong D, Devaney KL, Dubinsky M, Edwards C, Ellinghaus D, Ferguson LR, Franchimont D, Fransen K, Gearry R, Georges M, Gieger C, Glas J, Haritunians T, Hart A, Hawkey C, Hedl M, Hu X, Karlsen TH, Kupcinskas L, Kugathasan S, Latiano A, Laukens D, Lawrance IC, Lees CW, Louis E, Mahy G, Mansfield J, Morgan AR, Mowat C, Newman W, Palmieri O, Ponsioen CY, Potocnik U, Prescott NJ, Regueiro M, Rotter JI, Russell RK, Sanderson JD, Sans M, Satsangi J, Schreiber S, Simms LA, Sventoraityte J, Targan SR, Taylor KD, Tremelling M, Verspaget HW, De Vos M, Wijmenga C, Wilson DC, Winkelmann J, Xavier RJ, Zeissig S, Zhang B, Zhang CK, Zhao H, International IBDGC, Silverberg MS, Annese V, Hakonarson H, Brant SR, Radford-Smith G, Mathew CG, Rioux JD, Schadt EE, Daly MJ, Franke A, Parkes M, Vermeire S, Barrett JC, Cho JH. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 2012; **491**: 119-124 [PMID: 23128233 DOI: 10.1038/nature11582]

4 **Sokol H**, Conway KL, Zhang M, Choi M, Morin B, Cao Z, Villablanca EJ, Li C, Wijmenga C, Yun SH, Shi HN, Xavier RJ. Card9 mediates intestinal epithelial cell restitution, T-helper 17 responses, and control of bacterial infection in mice. *Gastroenterology* 2013; **145**: 591-601.e3 [PMID: 23732773 DOI: 10.1053/j.gastro.2013.05.047]

5 **Sokol H**, Leducq V, Aschard H, Pham HP, Jegou S, Landman C, Cohen D, Liguori G, Bourrier A, Nion-Larmurier I, Cosnes J, Seksik P, Langella P, Skurnik D, Richard ML, Beaugerie L. Fungal microbiota dysbiosis in IBD. *Gut* 2016; **pii**: gutjnl-2015-310746 [PMID: 26843508 DOI: 10.1136/gutjnl-2015-310746]

6 **Lee JS**, Cella M, McDonald KG, Garlanda C, Kennedy GD, Nukaya M, Mantovani A, Kopan R, Bradfield CA, Newberry RD, Colonna M. AHR drives the development of gut ILC22 cells and postnatal lymphoid tissues via pathways dependent on and independent of Notch. *Nat Immunol* 2011; **13**: 144-151 [PMID: 22101730 DOI: 10.1038/ni.2187]

7 **Hashimoto T**, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, Sigl V, Hanada T, Hanada R, Lipinski S, Wild B, Camargo SM, Singer D, Richter A, Kuba K, Fukamizu A, Schreiber S, Clevers H, Verrey F, Rosenstiel P, Penninger JM. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature* 2012; **487**: 477-481 [PMID: 22837003 DOI: 10.1038/nature11228]

8 **Kim CJ**, Kovacs-Nolan JA, Yang C, Archbold T, Fan MZ, Mine Y. l-Tryptophan exhibits therapeutic function in a porcine model of dextran sodium sulfate (DSS)-induced colitis. *J Nutr Biochem* 2010; **21**: 468-475 [PMID: 19428234 DOI: 10.1016/j.jnutbio.2009.01.019]

9 **Zelante T**, Iannitti RG, Cunha C, De Luca A, Giovannini G, Pieraccini G, Zecchi R, D'Angelo C, Massi-Benedetti C, Fallarino F, Carvalho A, Puccetti P, Romani L. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. *Immunity* 2013; **39**: 372-385 [PMID: 23973224 DOI: 10.1016/j.immuni.2013.08.003]

10 **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; **487**: 104-108 [PMID: 22722865 DOI: 10.1038/nature11225]

11 **Nikolaus S**, Al-Massad N, Bethge J, Waetzig GH, Rosenstiel PC, Junker R, Thieme F, Schreiber S. 2014 DDW AbstractSu1079 Tryptophan Deficiency in Crohn Disease. *Gastroenterology* 2014; **146**: S-366-S-367 [DOI: 10.1016/S0016-5085(14)61328-7]

12 **Rothhammer V**, Mascanfroni ID, Bunse L, Takenaka MC, Kenison JE, Mayo L, Chao CC, Patel B, Yan R, Blain M, Alvarez JI, Kébir H, Anandasabapathy N, Izquierdo G, Jung S, Obholzer N, Pochet N, Clish CB, Prinz M, Prat A, Antel J, Quintana FJ. Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. *Nat Med* 2016; **22**: 586-597 [PMID: 27158906 DOI: 10.1038/nm.4106]

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