EMBJ.ORG FOR YOUNG DOCTORS

EUROMEDITERRANEAN BIOMEDICAL JOURNAL
2017,12 (14) 066–068
(*FORMERLY: CAPSULA EBURNEA*)

Commentary

IMMUNOLOGICAL ASPECTS OF CROHN'S DISEASE: A REGULATORY FUNCTION OF TIM-3/ GALECTIN-9 IN LYTH1.

Francesco Carini [1], Carola Gagliardo [2], Margherita Mazzola [1,3], Elena Lo Presti [4,5], Marco Scaglione [2], Abdo Jurjus [6], Alice Gerges Geagea [1], Raymond Zerbe [6], Angelo Leone [7], Francesca Rappa [1], Sabrina David [1], Giovanni Tomasello [1*]*

[*] *These authors contributed equally to the present work.*

1. *Department of Experimental Biomedicine and Clinical Neuroscience, Section of Anatomy, (BIONEC), University of Palermo, Italy*
2. *Student of School of Medicine and Surgery, Palermo University, Italy.*
3. *Euro-Mediterranean Institute of Science and Technology (IEMEST), Palermo, Italy.*
4. *Central Laboratory of Advanced Diagnosis and Biomedical Research (CLADIBIOR), University of Palermo, Italy.*
5. *Department of Biopathology and Medical Biotechnologies (DIBIMED), University of Palermo, Italy.*
6. *Department of Anatomy, Cell Biology and Physiological Sciences, American University of Beirut. Beirut-Lebanon.*
7. *Department of Experimental Biomedicine and Clinical Neuroscience, Section of Histology, (BIONEC), University of Palermo, Italy.*

ARTICLE INFO

Article history:
Received 22 March 2017
Revised 25 April 2017
Accepted 01May 2017

Keywords:
Crohn's disease, Inflammatory Bowel Diseases, TIM-3/galectin-9.

ABSTRACT

Crohn's disease (CD) is a type of inflammatory bowel disease (IBD) and its etiology is multifactorial and involves a combination of genetic and environmental factors. The interaction of these factors causes an imbalance in the microbiota, leading to the activation of several immunological and inflammatory mechanisms. From an immunological point of view, there seems to be an involvement of the TIM-3/galectin-9 pathway and of the autoregulation of LyTh1. The studies show that in patients with CD the autoregulation of LyTh1 is lost due to a reduced concentration of galectin-9 and a reduced TIM-3 expression in LyTh1. This could be one of the reasons for the state of perpetual activation in LyTh1, resulting in the chronic inflammatory process.

1. Introduction

Crohn's disease (CD) is a type of inflammatory bowel disease (IBD), like ulcerative colitis (UC) and indeterminate colitis (IC). This disease is characterized by a chronic inflammatory process that can involve every segment of the digestive tract from the mouth to the anus; the last ileal loop is particularly susceptible to its effects. The chronic inflammatory process that occurs in CD leads to profound anatomical and functional changes of the mucosa, ranging from simple superficial ulcerations to perforations. The disease can cause various symptoms, such as abdominal pain, often bloody diarrhea, dehydration, intermittent and prolonged fever, malabsorption of nutrients, weight loss, and sometimes anemia. Further common complications include stenosis, fissures and perianal fistulas (1-4).

The etiology of CD is multifactorial and involves a combination of genetic and environmental factors. A current key point of interest is intestinal dysbiosis (5). Indeed, the intestinal microbiota of subjects with CD show a dysbiosis characterized by changes in *Firmicutes* and *Proteobacteria* phyla (6).

Dietary habits, such as a diet rich in sugars and fats (2,3), smoking (2,7), and use of antibiotics (8) are some of the environmental factors that can influence the composition of the intestinal microbiota. The interaction of these factors causes an imbalance in the microbiota, leading to the activation of several immunological and inflammatory mechanisms. Such

* *Corresponding author*: Francesco Carini, francesco.carini@unipa.it
DOI: 10.3269/1970-5492.2017.12.14
 ISSN: 2279-7165 - Available on-line at www.embj.org

mechanisms include the alteration of tight junctions in the intestinal epithelial barrier (9) and the establishment of a chronic inflammatory state, characterized by the release of various chemical mediators of inflammation, such as heat shock proteins (HSP), interleukins and COX-2 causing the release of arachidonic acid metabolites (10-14).
From an immunological point of view, there seems to be an involvement of the TIM-3/galectin-9 pathway, which will be discussed in detail below.

2. TIM-3/galectin-9 pathway and CD

The enzymes of enteric bacteria induce tight junction alterations in the epithelium of the intestinal mucosa, promoting the passage of bacteria to the lamina propria, where the gut-associated lymphoid tissue (GALT) is located (15). GALT contains different cell types that produce cytokines, which activate cells and determine the differentiation of naive T lymphocytes (LyT) into LyTh1, believed to be the main protagonists of the immune response in CD (16-18). LyTh1 produce interferon gamma (IFN-y) and matrix metallo proteinases (MMPs), which cause an amplified permeabilization of the epithelial barrier, thus intensifying the tissue damage and causing the inflammatory state to become chronic (15). The switch-off mechanism of LyTh1 is regulated through the interaction between two molecules produced by the lymphocytes themselves: a membrane protein called T-cell immunoglobulin and mucin domain, or TIM-3 and its ligand, a glycoprotein called galectin-9 (19). It has been shown that the interaction between TIM-3 and galectin-9 in LyTh1 downregulates the production of inflammatory cytokines, such as IFN-y, IL-17, IL-2, and IL-6 (12,13,20), by inducing peripheral tolerance (19) and mediating apoptosis inhuman and murine Th1 (21). However, the mechanisms through which TIM-3/galectin-9 interaction causes an increase in the transcription of cytokines and apoptosis of T-cells are still somewhat uncertain. Currently, it is thought that this interaction causes the entry of calcium into the cells, thus inducing apoptosis (22). The TIM-3/galectin-9 pathway appears to be an important factor in the pathogenesis of CD. TIM-3 is a surface molecules electively expressed in LyTh1 of the intestinal mucosa. Galectin-9 binding regulates these lymphocytes in the healthy mucosa. It has been observed that in patients with CD, the autoregulation of LyTh1 is lost due to a reduced concentration of galectin-9 and a reduced TIM-3 expression in LyTh1 (19). This could be one of the reasons for the state of perpetual activation in LyTh1, resulting in the chronic inflammatory process. This hypothesis opens up a possible pharmacological solution for disorders characterized by TIM-3/galectin-9 alterations, with the development of drugs targeted at increasing the amount of galectin-9 in patients with CD (23).

3. Conclusions

These data suggest that TIM-3 plays a pro-apoptotic role in immunosuppression and production of pro-inflammatory cytokines, dependent on the concentration of galectin-9. Based on these observations, drugs that induce the interaction between TIM-3 and galectin-9 could be created, aimed at reducing the inflammatory processes characteristic of CD, and the consequent chronicization. Further studies are needed to better determine the clinical and therapeutic aspects of TIM-3/galectin-9 binding.

References

1. Mazzola M, Carini C, Leone A, Damiani P, Messina M, Jurjus A, Gerges Geagea A, Jurjus R, Tomasello G. IBD, malignancy and oral microbiota: analysis of literature. International Journal of Clinical Dentistry 2016;9(9):273-278.
2. Mazzola M, Carini F, Leone A, Damiani P, Jurjus A, Gerges Geagea A, Jurjus R, Bou Assi T, Trovato E, Rappa F, Tomasello G. Inflammatory bowel disease and colorectal cancer, nutraceutical aspects. Euromediterranean biomedical journal 2016; 11(17):123-129.
3. Tomasello G, Mazzola M, Leone A, Sinagra E, Zummo G. Farina F, Damiani P, Cappello F, Gerges Geagea A, Jurjus A, Bou Assi T, Messina M, Carini F. Nutrition, oxidative stress and intestinal dysbiosis: Influence of diet on gut microbiota in inflammatory bowel diseases. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2016; 160(4):461-466.
4. Carini F, Sanfilippo A, Margiotta G, Mazzola M, Scardina GA, Messina M. Rappa F, Trovato E, Damiani P, Tomasello G. Inflammatory bowel disease and peripheral arthritis: mesalazina and probiotics. Euromediterranean biomedical journal 2016; 11(15):112-117.
5. Chassaing B, Darfeuille-Michaud A. The commensal microbiota and enteropathogens in the pathogenesis of inflammatory bowel diseases. Gastroenterology 2011;140(6):1720-28.
6. Morgan XC, Tickle TL, Sokol H, Gevers D, Devaney KL, Ward DV, Reyes JA, Shah SA, LeLeiko N, Snapper SB, Bousvaros A, Korzenik J, Sands BE, Xavier RJ, Huttenhower C. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. Genome Biol 2012;13(9):R79.
7. Benjamin JL, Hedin CR, Koutsoumpas A, Ng SC, McCarthy NE, Prescott NJ, Pessoa-Lopes P, Mathew CG, Sanderson J, Hart AL, Kamm MA, Knight SC, Forbes A, Stagg AJ, Lindsay JO, Whelan K. Smokers with active Crohn's disease have a clinically relevant dysbiosis of the gastrointestinal microbiota. Inflamm Bowel Dis 2012;18(6):1092-100.
8. Hviid A, Svanström H, Frisch M. Antibiotic use and inflammatory bowel diseases in childhood. Gut 2011;60(1):49-54.
9. Tomasello G, Tralongo P, Damiani P, Sinagra E, Di Trapani B, Zeenny MN, Hussein IH, Jurjus A, Leone A.Dismicrobism in inflammatory bowel disease and colorectal cancer: changes in response of colocytes. World J Gastroenterol 2014;20(48):18121-30.
10. Rappa F, Sciume C, Lo Bello M, Bavisotto CC, Marino Gammazza A, Barone R, Campanella C, David S, Carini F, Zarcone F, Rizzuto S, Lena A, Tomasello G, Uzzo ML, Spatola GF, Bonaventura G, Leone A, Gerbino A, Cappello F, Bucchieri F, Zummo G, Farina F. Comparative analysis of Hsp10 and Hsp90 expression in healthy mucosa and adenocarcinoma of the large bowel. Anticancer Res 2014;34(8):4153-9.
11. Cappello F, Conway de Macario E, Marino Gammazza A, Bonaventura G, Carini F, Czarnecka AM, Farina F, Zummo G, Macario AJ. Hsp60 and human aging: Les liaisons dangereuses. Front Biosci (Landmark Ed) 2013;18:626-37.
12. Scardina GA, Pisano T, Carini F, Valenza V, Messina P.Burning mouth syndrome: an evaluation of in vivo microcirculation.J Am Dent Assoc 2008;139(7):940-6.
13. Mesa F, O'Valle F, Rizzo M, Cappello F, Donos N, Parkar M, Chaudhary N, Carini F, Muñoz R, Nibali L.Association between COX-2 rs 6681231 genotype and interleukin-6 in periodontal connective tissue. A pilot study.PLoS One 2014;9(2):e87023.

14. Scardina GA, Cacioppo A, Carini F, Ruggieri A, Valenza V, Messina P. Periodontal morphological microcirculation in oral lichen planus**.**J Anat Embryol 2007; 112(4):281 – 292.

15. Boyapati R, Satsangi J, Ho G-T. Pathogenesis of Crohn's disease. F1000Prime Rep 2015;7:44.

16. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-Y M, Glickman JN, Garrett WS.The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis.Science 2013;341(6145):569-73.

17. Monteleone G, Biancone L, Marasco R, Morrone G, Marasco O, Luzza F, Pallone F.Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. Gastroenterology 1997;112(4):1169-78.

18. Pizarro TT, Michie MH, Bentz M, Woraratanadharm J, Smith MF Jr, Foley E, Moskaluk CA, Bickston SJ, Cominelli F.IL-18, a novel immunoregulatory cytokine, is up-regulated in Crohn's disease: expression and localization in intestinal mucosal cells.J Immunol 1999;162(11):6829-35.

19. Morimoto K, Hosomi S, Yamagami H, Watanabe K, Kamata N, Sogawa M, Machida H, Okazaki H, Tanigawa T, Nagahara H, Noda E, Tominaga K, Watanabe T, Fujiwara Y, Maeda K, Hirakawa K, Arakawa T.Dysregulated upregulation of T-cell immunoglobulin and mucin domain-3 on mucosal T helper 1 cells in patients with Crohn's disease.Scand J Gastroenterol 2011;46(6):701-9.

20. Sabatos CA, Chakravarti S, Cha E, Schubart A, Sánchez-Fueyo A, Zheng XX, Coyle AJ, Strom TB, Freeman GJ, Kuchroo VK.Interaction of Tim-3 and Tim-3 ligand regulates T helper type 1 responses and induction of peripheral tolerance.Nat Immunol 2003;4(11):1102-10.

21. Hastings WD, Anderson DE, Kassam N, Koguchi K, Greenfield EA, Kent SC, Zheng XX, Strom TB, Hafler DA, Kuchroo VK.TIM-3 is expressed on activated human CD4+ T cells and regulates Th1 and Th17 cytokines.Eur J Immunol 2009;39(9):2492-501.

22. Rabinovich GA, Liu FT, Hirashima M, Anderson A.An emerging role for galectins in tuning the immune response: lessons from experimental models of inflammatory disease, autoimmunity and cancer.Scand J Immunol 2007;66(2-3):143-58.

23. Zhu C, Anderson AC, Schubart A, Xiong H, Imitola J, Khoury SJ, Zheng XX, Strom TB, Kuchroo VK.The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity.Nat Immunol 2005;6(12):1245-52.