UPDATE ON INFLAMMATORY BOWEL DISEASES ETHIOPATOGENICS

Alexandru LUPU[1]
Cosmin CIORA[2]
Mircea DICULESCU[3]

ABSTRACT
THE INFLAMMATORY BOWEL DISEASES (IBD) CROHN'S DISEASE (CD) AND ULCERATIVE COLITIS (UC) ARE CHRONIC IMMUNOLOGIC DISEASES THAT CAN LEAD TO DECREASED QUALITY OF LIFE AND INVALIDITY; IBD ARE CHARACTERIZED BY ABERRANT IMMUNE RESPONSES TO INTESTINAL MICROBIOTA IN GENETICALLY SUSCEPTIBLE HOSTS THAT LEAD TO CHRONIC EXCESSIVE INFLAMMATION AND IN TIME TO PROGRESSIVE GUT WALL DESTRUCTION. IBD HAVE AN EUROPEAN INCIDENCE OF 12 TO 25 PER 100,000 PERSON-YEARS, HIGHER FOR UC THAN CD, WITH A PREVALENCE OF 0.5-1%.
ENVIRONMENTAL FACTORS LIKE CIGARETTE SMOKING, POLLUTION, CHANGES IN DIET AND EXCESSIVE USE OF ANTIBIOTICS ARE INCRIMINATED IN IBD PATOGENESIS.
THERE IS THOUGHT TO EXIST AN IMBALANCE IN THE INNATE AND ACQUIRED IMMUNE RESPONSES TO NORMAL INTESTINAL MICROBIOTA THAT ACTIVATES PRO-INFLAMMATORY CYTOKINES AND LEADS TO A CHRONIC INFLAMMATORY PROCESS AROUND THE GUT BARRIER. THIS IN TIME LEADS TO INTESTINAL BARRIER DESTRUCTION AND EXPOSURE TO EVEN MORE BACTERIAL PARTICLES THAT FURTHER AGGRAVATE THE INFLAMMATORY PROCESS.
GENETIC STUDIES HAVE PROVIDED MANY SUSCEPTIBLE LOCI FOR IBD. IT IS KNOWN FROM THE LITERATURE THAT GENETIC FACTORS ACCOUNT FOR 13.6% OF CD AND 7.5% FOR UC VARIANCE.
IN THIS LITERATURE REVIEW WE HIGHLIGHT SOME ETHIOPATHOGENIC LEADS THAT ARE RECENT TARGETS OF CLINICAL AND FUNDAMENTAL IBD RESEARCH.

KEY WORDS: IBD GENETICS, IMMUNOLOGY, THERAPEUTIC TARGETS

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory immune mediated diseases that affect genetic predisposed individuals and can interfere with quality of life and working ability. Inflammatory bowel disease's (IBD) incidence in Europe is 12.7 (CD) and 24.3 (UC) per 100,000 person-years while prevalence is around 0.5-1% [1].

In genetically susceptible individuals the relationship between aberrant immune responses and intestinal microbiota, that can be changed by diet habits [2], leads to gut barrier

[1] MD. PhD Student, Departament of Gastroenterology and Hepatology, Fundeni Clinical Institute, Bucharest, alexandru.c.lupu@gmail.com
[2] MD. PhD Student, Departament of Gastroenterology and Hepatology, Fundeni Clinical Institute, Bucharest
[3] Prof. PhD, Departament of Gastroenterology and Hepatology, Fundeni Clinical Institute, Bucharest

destruction and higher permeability for pathogenic bacteria. This attracts in time chronic inflammation, edema, erosion and ulcerations that can manifest with fatigue, abdominal pain, weight loss and chronic bloody diarrhea. Due to a high variability and multiple pathogenic mechanisms there is still no clear etiopatogenic mechanism of IBD.

MAIN TEXT

1. Environmental factors have an important role in IBD patogenesis, for example cigarette smoking is a known risk factor for CD because it interferes with the function of NOD2 gene [3]. There is also a north-south, west-east prevalence gradient in IBD that is probably due to environmental factors and diet. Current theories support the fact that an active hygiene, secondary to the high standard of life in western society, leads to a lower exposure to bacterial antigens in childhood and a higher incidence of IBD [4]. Changing nutrition habits in infants with decreasing breast feeding (known to be a protective factor), excess of antibiotic regimes, proton pump inhibitors and western diet rich in processed food, fat, animal proteins and polyunsaturated fatty acids and low in vegetables, fiber and fruits play an important role in changing intestinal microbiota [5] and increasing IBD prevalence.

2. Unlike general population, IBD patients have an aberrant immunologic response to external antigenic stimuli that is increased in duration and severity [6]. Alterations in gut wall start by loss of tight junctions between epithelial cells and destruction of mucosal layer witch increases intestinal permeability to luminal bacterial antigens [7].

This alterations are further amplified by loss of inhibitory immune mechanisms, macrophages and numerous pro-inflammatory cytokines activation. Until recently we considered that immune reaction to antigens was different in CD as opposed to UC. In CD there was a lymphocyte T helper 1 (Th1) mediated reaction that differed to the Th2 activation seen in UC patients. A new pathogenic theory common for both CD and UC shows that the hyperactivity of cellular immune response is mediated by the presence of Th17 lymphocytes that are implicated in the secretion of numerous cytokines: interleukin (IL) 17, IL 22, IL 23, IL 26 [8][9][10].

There is another theory that the chronic inflammation in IBD is secondary to an energy imbalance. This imbalance is due to alterations in the oxidative metabolism from the intestinal epithelial cells [11][12] and to cell-specific endoplasmic reticulum (ER) stress which induces dysfunctions in Paneth cells, goblet cells that produce mucus and that alters the enterocyte barrier [13][14]. The ER stress contributes to pathogenic mechanisms of insulin-resistance in type 2 diabetes and this proves that there is o common pathogenic way in both IBD and metabolic diseases [15].

Mitochondria are essential cellular organelles for maintaining energetic equilibrium by adenosine triphosphate (ATP) mediated energy intake, apoptosis regulation and oxygen free radicals production. The paper published by Bertran and his collegues prooves that excessive levels of oxidized molecules, inhibited mitochondria and hypersensitivity to oxidative stress are implicated in IBD pathogenesis [16].

3. Genetic susceptibility in IBD patients was demonstrated in numerous genome-wide association studies. Nevertheless, it has been proven that there is no simple model, Mendelian type, that could explain IBD transmission. Mono-zygotic twins have up to 67% concordance for developing CD [17] and 15-20% for UC. By genotyping, in the last years there have been found numerous susceptibility loci associated with IBD. There are more than 40 confirmed loci and over 160 susceptibility loci [18]. Most of the confirmed loci are common for CD and UC like the genes for lymphocyte Th 17 mediated immune response (IL23R, IL12B, JAK 2, STAT 3) [19][20]. The genes that differ between the two IBD's are a good premise for future research and new therapeutic molecules, specific for each inflammatory bowel disease in

part. Crohn's disease is associated with autophagocytosis genes: ATG16L1, IRGM and NOD2 while UC genetic specificity is in relation to the genes that codify the gastro-intestinal epithelial barrier: HNF4a, E-caderin, LAMB 1 and IL 10 [21]. It's interesting that some genes like NOD 2 and PTPN22 predispose to CD but are a protective genetic element against UC. By genotyping rises the posibility to discover new molecules that are specific for each IBD patogenesis in part and also the posibility to identify genetic markers that are able to predict disease outcome and therapeutic response. A recent study identified mutations that are part of NFkB inflammatory path; this particular mutations can predict the rate of response to anti tumor necrosis factor alfa (anti-TNF α) molecules - a very potent immunosupressant class of drugs [22]. Bank S. et al paper also identified new possible therapeutic targets (IL 1β, IL-6, IFN-γ) that can become very useful in the future.

4. IBD patients have a particular intestinal microbiota: a decrease in non-patogenic species like Bifidobacteria, Lactobacili and Firmicutes and an increase in patogenic species like Bacteroides and Escherichia coli [23]. In healthy subjects autophagy mechanisms are efficient enough to eliminate intracellular pathogens from digestive tract but Hang Thi Thu Nguyen and his colleagues have recently demonstrated that in CD patients Adherent Invasive Escherichia coli (AIEC) suppresses autophagy gene expression (ATG 5, ATG16L1) and that leads to the inability of clearing this bacteria from the intracellular space [24]. AIEC persistance maintains a chronic inflammatory intestinal process with excesive pro-inflammatory cytokines. This is just one of the papers that highlights the importance of gut microbiota in IBD ethiopathogenic mechanisms and the utility of prebiotics and probiotics to obtain and maintain disease remission. Also, microbiota pathological diversity in CD and UC is reason to justify increasingly more often fecal transplant as a new way to treat selected IBD patients.

CONCLUSIONS

Even though all this etiopathogenic leads are valuable therapeutic targets for fundamental and clinical gastroenterology, immunology and genetics research we are still far away from the moment when finding "a cause and one etiologic treatment" for all IBD forms and patients.

General diversity of etiopathogenic mechanisms as well as global heterogeneity of IBD makes mandatory permanent literature update for every IBD specialist and also underlines the need to better understand local geographical particularities and trends in Crohn's disease and ulcerative colitis.

ACKNOWLEDGEMENTS

- this study was supported by the Sectorial Operational Programme Human Resources Development (SOP HRD) financed from the European Social Fund and by the Romanian Government under the contract POSDRU/107/1.5/S/82839

REFERENCES

1. **Molodecky NA, Soon IS, Rabi DM, et al.** Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology.* 2012, 142: 46-54.
2. **Viladomiu M et al.** Nutritional protective mechanisms against gut inflammation. *Journal of Nutritional Biochemistry.* 2013, 24(6):929-39.
3. **Aldhous MC, Soo K, Stark LA, et al.** Cigarette smoke extract (CSE) delays NOD2 expression and affects NOD2/RIPK2 interactions in intestinal epithelial cells. *PloS One.* 2011, 6:e24715.
4. **Cucino C, Sonnenberg A.** Occupational mortality from inflammatory bowel disease in the United States 1991-1996. *Am J Gastroenterol.* 2001, 96:1101-05.
5. **Jason K Hou, Bincy Abraham, Hasem El-Serag.** Dietary Intake and Risk of Developing Inflammatory Bowel Disease: A Systematic Review of the Literature. *Am J Gastroenterol.* 2011, 106:563-73.
6. **Mark Feldman, Lawrence S. Friedman, Lawrence J. Brandt (Eds.).** *Sleisenger and Fordtran's Gastrointestinal and Liver Disease.* New York : Sounders Elsevier, 2010. ISBN: 9-7814-1606-1892.
7. **Gerova VA, Stoynov SG, Katsarov DS, Svinarov DA.** Increased intestinal permeability in inflammatory bowel diseases assessed by iohexol test. *World J Gastroenterol.* 2011, 17:2211-15.
8. **Kobayashi T, Okamoto S, Hisamatsu T et al.** IL23 differentially regulates the Th1/Th17 balance in ulcerative colitis and Crohn's disease. *Gut.* 2008, 57: 1682-89.
9. **Dige A, Stoy S, Rasmussen TK et al.** Increased levels of circulating Th17 cells in quiescent versus active Crohn's disease. *J Crohns Colitis.* 2013, 7: 248-55.
10. **Xu XR, Liu CQ, Feng BS, Liu ZJ.** Dysregulation of mucosal immune response in pathogenesis of inflammatory bowel disease. *World J Gastroenterol.* 2014, 20(12):3255-64.
11. **Roediger WE.** The colonic epithelium in ulcerative colitis: an energy-deficiency disease? *Lancet.* 1980, 2: 712-5.
12. **Fukushima K, Fiocchi C.** Paradoxical decrease of mitochondrial DNA deletions in epithelial cells of active ulcerative colitis patients. *Am J Physiol Gastrointest Liver Physiol.* 2004, 286: G804 13.
13. **Shkoda A, Ruiz PA, Daniel H, Kim SC, Rogler G, Sartor RB, Haller D.** Interleukin-10 blocked endoplasmic reticulum stress in intestinal epithelial cells: impact on chronic inflammation. *Gastroenterology.* 2007, 132: 190 207.
14. **Kaser A, Lee AH, Franke A, Glickman JN, Zeissig S, Tilg H, Nieuwenhuis EE, Higgins DE, Schreiber S, Glimcher LH, Blumberg RS.** XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease. *Cell.* 2008, 134: 743-56.
15. **Hotamisligil GS, Erbay E.** Nutrient sensing and inflammation in metabolic diseases. *Nat Rev Immunol.* 2008, 8: 923-34.
16. **Beltran B, Nos P, Dasi F et al.** Mitochondrial dysfunction, persistent oxidative damage, and catalase inhibition in immune cells of naive and treated Crohn's disease. *Inflamm Bowel Dis.* 2010, 16: 76-86.
17. **Dorn SD, Abad JF, Panagopoulos G, Korelitz BI.** Clinical characteristics of familial versus sporadic Crohn's disease using the Vienna Classification. *Inflamm Bowel Dis.* 2004, 10:201-6.
18. **Jostins L, Ripke S, Weersma RK, et al.** Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature.* 2012, 490:119-24.
19. **Anderson CA, Boucher G, Lees CW, et al.** Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nat Genet.* 2011, 43:246-52.
20. **Brand S.** Crohn's disease: Th1, Th17 or both? The change of a paradigm: new immunological and genetic insights implicate Th17 cells in the pathogenesis of Crohn's disease. *Gut.* 2009, 58:1152-1167.
21. **Parkes M.** Advances in IBD genetics and clinical implications. *Journal of Crohn's and Colitis Supplements.* 2010, Vol. 4, 1: 3-4.
22. **Bank S, Andersen PS, Burisch J et al.** Associations between functional polymorphisms in the NFκB signaling pathway and response to anti-TNF treatment in Danish patients with inflammatory bowel disease. *Pharmacogenomics J.* 2014, 14(6):526-34.
23. **Chassaing B, Darfeuille-Michaud A.** The commensal microbiota and enteropathogens in the pathogenesis of inflammatory bowel diseases. *Gastroenterology.* 2011, 140: 1720-28.
24. **Hang Thi Thu Nguyen et al.** Crohn's Disease-Associated Adherent Invasive Escherichia coli Modulate Levels of microRNAs in Intestinal Epithelial Cells to Reduce Autophagy. *Gastroenterology.* 2014, 146: 508-19.

INFORMATION ABOUT RESEARCH AND SCIENCE TODAY JOURNAL

AIMS AND SCOPE OF THE CONTENT

Research and Science Today Journal is a publication founded in 2011 and it is dedicated to the students of all levels (license, master and doctoral), professors and researchers of faculties in the country and abroad. We want to offer the participants the opportunity to present their scientific works in the following areas: Social Sciences, Economic Sciences, Legal Sciences, Humanities, Education Sciences, Engineering, Medicine and Sport.
This journal provides students the opportunity to create and / or to improve their abilities to write scientific papers. So each appearance (two appearances per year at which we can add supplements) contains a number of papers written by students, masters and doctoral from the faculties from the country or / and abroad. The journal promotes original studies contributing to the progress of knowledge and it is motivated by the need to address issues of theory and practice in the areas mentioned above.
The Journal is a training means of the factors involved in the conceptualization, development, implementation and evaluation, aiming the formation of creative personalities who could be able to adapt through the changing conditions of life.
Journal wants to be a forum for debates disciplinaries and interdisciplinaries theoretical topics, to become a research support, to leverage this work at regional, national and international levels.
We believe that this gathering will enjoy the support from both parts of the researchers and of the practitioners, and will provide appropriate training sources held professional through the current problems.
Frequency of publication: 2 number per year (March and November) and supplement numbers (if it necessary)
Peer-review process: All submitted manuscripts are peer-reviewed by members of the Editorial Board. Papers that fit to the topic of the journal are evaluated by two independent scientific reviewers who accepted to review papers and sent to the Editor in Chief the Reviewer Invitation Response Form. Reviewers' identity is undisclosed to the authors.
Reviewers give to the Editor in Chief their Form for Reviewer, with the comments on the scientific content of the paper and on the opportunity of publishing it. Editor in Chief summarizes reviewers' observations in order to be communicated to the corresponding author. Taking into account the opinions of all referees, the Editor in Chief decides on the acceptance/revision/rejection of the paper. Upon reviewers' recommendations, the manuscript can be accepted, sent back to author for minor revisions, or rejected.
Abstracting and indexing: SSRN, EBSCO, ProQuest, IndexCopernicus, Scipio, Genamics, Ulrich`s Periodicals Directory, DOAJ, MPRA (Ideas, EconPapers, Socionet), HeinOnline, Google Academic, DRJI, CiteFactor.
More informations here: http://www.rstjournal.com/indexari-2/

CONTACT:
Phone: +40766665670
Mail: revistarst@yahoo.com
Web: http://www.rstjournal.com